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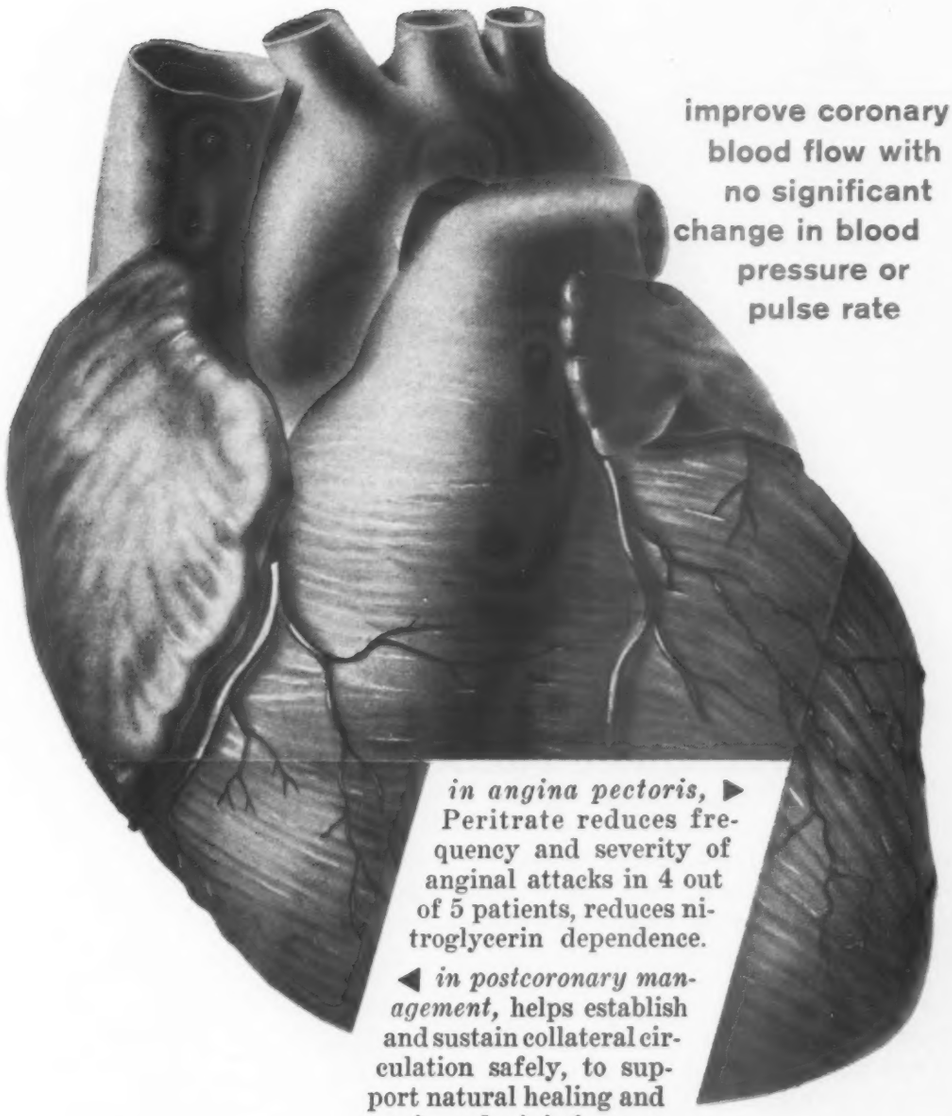
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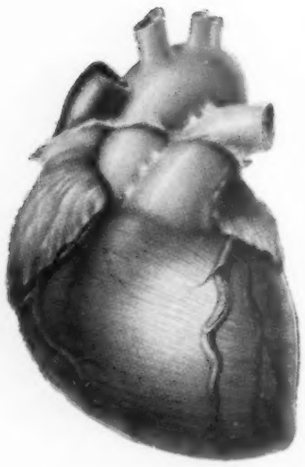
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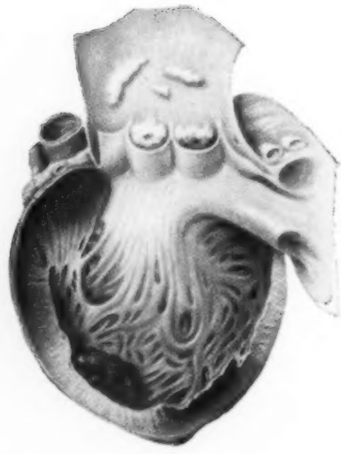
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1. Ellis, L. B. *et al.:* Circulation *17*:945, May 1958. **2.** Friedlander, H. S.: Am. J. Cardiol. *1*:395, Mar. 1958. **3.** Riseman, J. E. F.: New England J. Med. *261*:1017, Nov. 12, 1959. **4.** Russek, H. I. *et al.:* Circulation *12*:169, Aug. 1955. **5.** Russek, H. I.: Am. J. Cardiol. *3*:547, April 1959. **6.** Tortora, A. R.: Delaware M. J. *30*:298, Oct. 1958. **7.** Waldman, S. and Pelner, L.: Am. Pract. & Digest Treat. *8*:1075, July 1957.

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The American Journal of Medicine

Vol. XXIX SEPTEMBER 1960 No. 3

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Current Status of Steroid Therapy in Chronic Glomerulonephritis in the Adult. The Unnatural History of Bright's Disease
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Hypoalbuminemia (with Anasarca) Due to Hypercatabolism, Serum Protein Exudation into the Gastrointestinal Tract, Increased Capillary Permeability and Hypoanabolism. The Unusual Occurrence of Increased Capillary Permeability Temporarily Reversed by Human Growth Hormone Therapy
Paul A. M. Gross, Laurence J. Embree, Peter Bally, Joseph C. Shipp and George W. Thorn 386

An exhaustive study of a patient with idiopathic hypoproteinemia revealed how complex the pathogenesis of hypoproteinemia may be under circumstances in which the only structural abnormality of any significance was nondescript thickening and edema of the small intestinal and gastric mucosa. Four mechanisms participated: exudation of plasma proteins into the gut, hypercatabolism of serum albumin, reduced biosynthesis of serum albumin, and increased peripheral capillary permeability with leakage of serum albumin into the extravascular compartment. Among the interesting observations made in this case was a startling but very transient increase in the otherwise refractorily low serum albumin levels when human growth hormone was given, apparently as a result of a temporary decrease in capillary loss of serum proteins.

The Mechanism of Hypoproteinemia in Patients with Regional Enteritis and Ulcerative Colitis
J. L. Steinfeld, J. D. Davidson, R. S. Gordon, Jr. and F. E. Greene 405

The hypoalbuminemia commonly occurring in regional enteritis and ulcerative colitis is generally ascribed to an absorptive defect for nitrogenous serum albumin precursors and/or to impaired biosynthesis because of accompanying malnutritional hepatic damage. The present study excluded the latter possibility in the subjects investigated, by demonstrating abnormally rapid removal of I^{131}-albumin from the circulating plasma and, indeed, a greater than normal rate of serum albumin synthesis. It could be shown further, by ingenious methodology, that the major cause of the low serum albumin in these patients is excessive loss of protein into the intestinal tract, a factor in depletion of protein stores which looms ever larger as the study of gastrointestinal lesions progresses.

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*Miller, J.B., et al.: Ann. Allergy, 12:611, Sept.-Oct., 1954.

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Amyloidosis in Regional Enteritis. A Report of Five Cases
J. Lawrence Werther, Adolfo Schapira, Oswaldo Rubinstein and Henry D. Janowitz 416

The experience thus far indicates that amyloidosis occurs as a complication of regional enteritis more frequently than in association with ulcerative colitis, despite the general impression to the contrary. This paper describes five such cases in which, interestingly enough, the development of amyloidosis could not be ascribed to unusual gross suppuration or fistula formation in connection with the underlying disease.

Trypsin, Trypsinogen and Trypsin Inhibitor in Human Pancreatic Juice. Mechanism for Pancreatitis Associated with Hyperparathyroidism
Bernard J. Haverback, Barbara Dyce, Hallie Bundy and Hugh A. Edmondson 424

The authors record experiments on factors operating in the activation of trypsinogen to trypsin, a process which presumably is responsible for the development of acute pancreatitis when it occurs prematurely in the pancreas or pancreatic ducts. Of interest in this reaction is the role of as yet unidentified inhibitors, and the action of calcium ion in various concentrations within the range of pathophysiological variation. The conversion of trypsinogen to trypsin is sufficiently accelerated by an increase in calcium to suggest this as a possible explanation of the occasional occurrence of acute pancreatitis in hyperparathyroidism.

Value of Splenic Portography in the Diagnosis of Intrahepatic and Extrahepatic Neoplasm
Francis F. Ruzicka, Jr., Capt. Howard R. Gould, Edward G. Bradley and Louis M. Rousselot 434

Serial percutaneous splenic portography may reveal primary and secondary neoplasms of the liver, as well as impingement upon the portal or splenic vein by tumor. The method is exacting, and may fail for technical or other reasons, but can give information not otherwise obtainable, as the illustrative films here shown clearly indicate.

Clinical and Laboratory Studies of Plasma Thromboplastin Antecedent Deficiency (PTA) . . . . . John A. Cavins and Robert L. Wall 444

Plasma thromboplastin antecedent deficiency has been regarded as a rare and rather innocuous member of the "hemophilioid" group of bleeding disorders but this study indicates that PTA deficiency is neither as rare nor always as mild as has been thought.

Further Observations on Leukoagglutinin Transfusion Reactions. With Special Reference to Leukoagglutinin Transfusion Reactions in Women
Rose Payne and Mary R. Rolfs 449

The role of leukoagglutinins in febrile and/or allergic transfusion reactions has only recently been appreciated but, as this study amply attests, is an important consideration because of the

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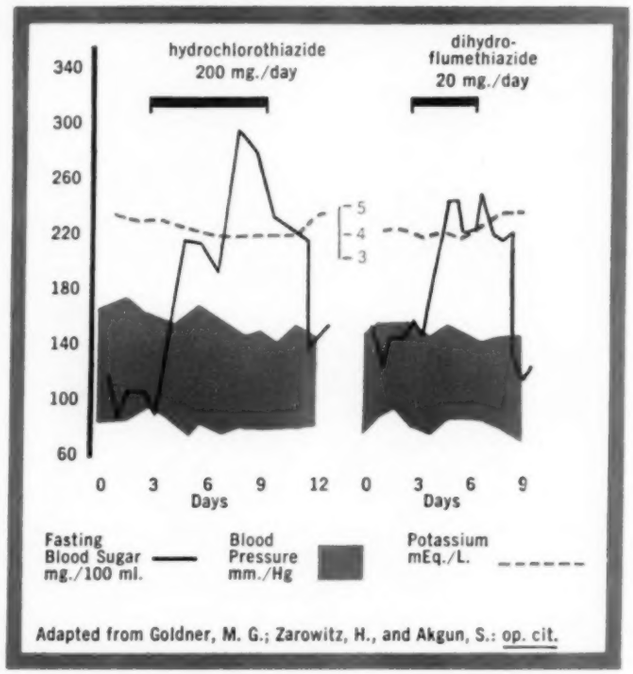
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Source:
Goldner, M. G.; Zarowitz, H., and Akgun, S.: New England J. Med. *262*:403, 1960.

EFFECT OF THIAZIDE THERAPY ON SUSCEPTIBLE DIABETIC PATIENT



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*Ackerman, R. F.; Williams, E. F., Jr.; Packer, H.; Hawkes, J. H., and Ahler, J.: Diabetes 7:398, 1958.

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prevalence of such reactions, particularly in women. This predilection for women, even after one or two transfusions, is best explained by fetal leukocyte stimulation, as the authors make clear. This type of transfusion reaction can be avoided by the use of blood from which most of the leukocytes have been removed. Both the testing of recipient and donor blood and leukocyte removal are entirely feasible for blood bank operation.

Pituitary-Adrenal Function Following Long-Term Steroid Therapy
J. WILLIAM MEAKIN, MARIA S. TANTONGCO, JEAN CRABBÉ, THEODORE B. BAYLES AND DON H. NELSON 459

While discontinuance of therapy with corticosteroids in patients who have received them for long periods has not proved as hazardous as was once feared, adrenocortical atrophy may present serious problems which are here subjected to analysis. It is shown that whereas pituitary function in respect to secretion of ACTH recovers fairly rapidly, the adrenocortical response lags behind, sometimes for months. The methods used to demonstrate these relationships are of considerable interest, as are the physiological implications.

Recurrent Attacks of Bacterial Meningitis. A "New" Clinical Problem. Report of Five Cases . . . . . JOHS. BØE AND HARALD HUSEKLEPP 465

This instructive report, of special interest in our age of increasingly frequent traffic accidents, deals with recurrent bacterial meningitis as the most prominent manifestation, indeed often the only manifestation, of occult skull fracture with persistent craniopharyngeal fistula. Five such cases are cited. They make clear the difficulties in diagnosis in some such cases, arising from the long asymptomatic interval which may elapse between trauma and meningitis, the not infrequent absence of any indication of fracture in skull roentgenograms, and the often inapparent fistula. Since surgical intervention offers the only certain cure, exploration is justified when the history and course are characteristic, even when the fracture and/or craniopharyngeal fistula cannot be demonstrated.

Familial Myocardial Disease. A Report of Three Siblings, and a Review of the Literature
OSCAR C. BEASLEY, JR. 476

A difficultly diagnosed and uncommon form of primary myocardial disease, of obscure pathogenesis, is one which is familial in occurrence and presumably due to some inborn error of myocardial metabolism. The clinical course follows a pattern which can be recognized, however, and is here well described. The author records three such cases occurring in siblings, which appear to fall into this pattern.

Reviews

Mechanisms of Salt and Water Retention in Congestive Heart Failure. The Importance of Aldosterone . . . . . JAMES O. DAVIS 486

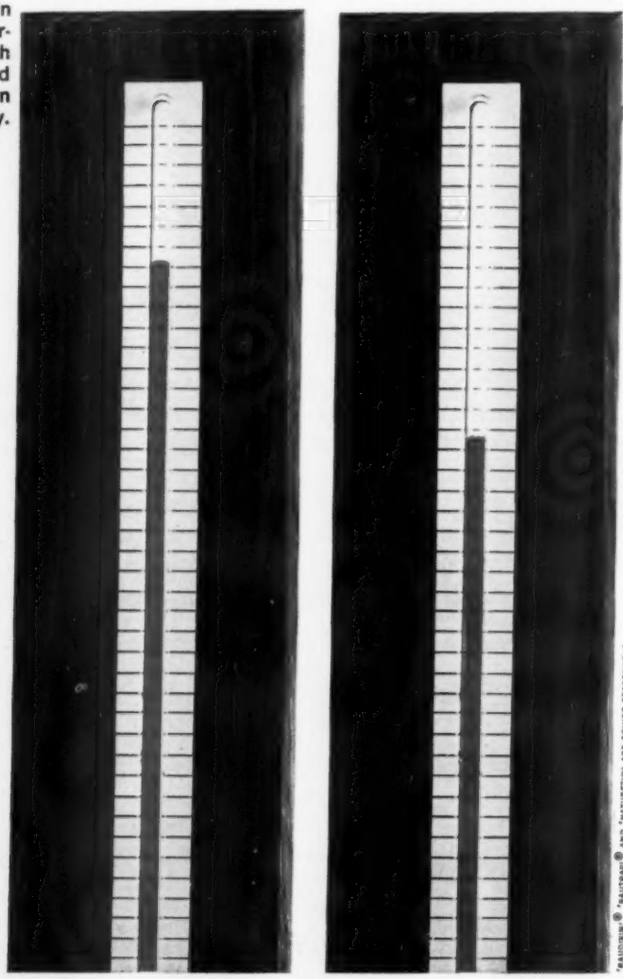
A consideration of the most recent evidence concerning the nature and sequence of the events leading from myocardial failure to edema formation suggests, according to the author, a partial synthesis of the concepts of "backward" and "forward" failure. The increased hydrostatic pres-

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sure of elevated venous pressure favors the outward movement of fluid and electrolytes from the vascular bed. It is this initial translocation, probably, that stimulates the adrenal cortex to increased secretion of aldosterone; by precisely what regulatory mechanisms is not known, although a number of more or less plausible possibilities are discussed. The immediate stimulus to increased aldosterone production appears to be humoral, specifically the hormone "glomerulotropin." In any event, the retention of sodium and water in congestive heart failure may now be ascribed with some assurance to increased circulating levels of aldosterone. Changes in glomerular filtration rate in relation to cardiac output and renal blood flow also play an important role.

Traumatic Asphyxia . . CAPT. HERBERT L. FRED AND MAJ. FRANK W. CHANDLER 508

Traumatic asphyxia is a rare but unforgettable clinical syndrome produced by crushing injuries to the thorax or upper part of the abdomen; recognition is obvious if one is at all familiar with the clinical picture, here fully described. The authors present a well studied case and give a detailed review of the literature. "Asphyxia" may be an unfortunate term since the facial discoloration is due to ecchymosis and congestion, moreover, it is not relieved by oxygen.

Clinicopathologic Conference

Dysphagia, Melena, Uremia and Hypertension in an Aged Patient 518

Clinicopathologic Conference (Washington University School of Medicine).

Case Reports

Pancreatic Islet Tumor with Severe Diarrhea
W. CROCKETT CHEARS, JR., JESSE E. THOMPSON, JAMES B. HUTCHESON AND CECIL O. PATTERSON 529

A case of unusual interest and difficulty in which a suspected pancreatic islet tumor was removed with complete recovery of the moribund patient.

Primary Myoglobinuria (Meyer-Betz Disease) . . . . . H. BRUCE DENSON 534

A lucid presentation of an interesting disorder, with an illustrative case.

Nephrogenic Diabetes Insipidus Caused by Amyloid Disease. Evidence in Man of the Role of the Collecting Ducts in Concentrating Urine
FRANK A. CARONE AND FRANKLIN H. EPSTEIN 539

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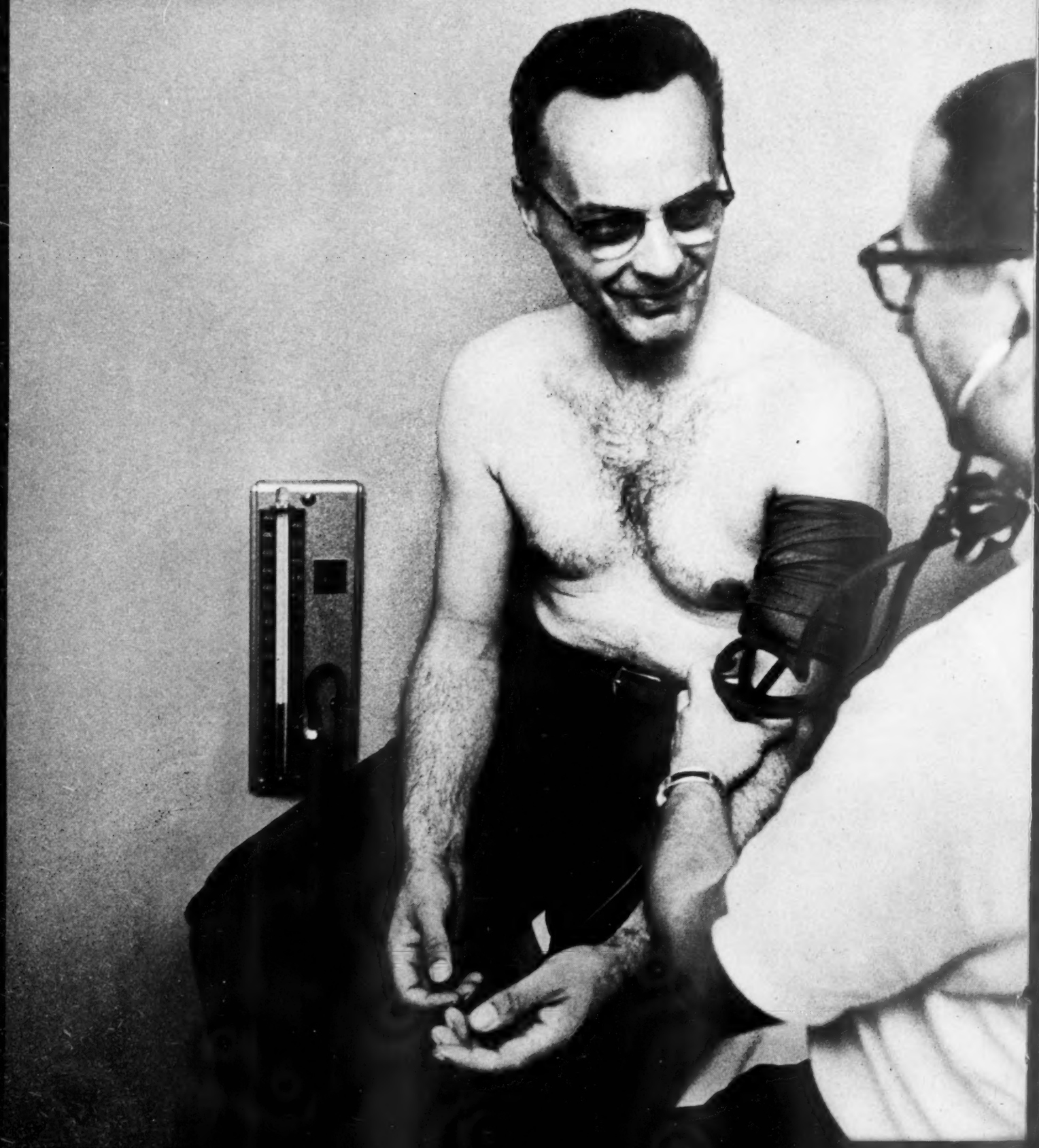
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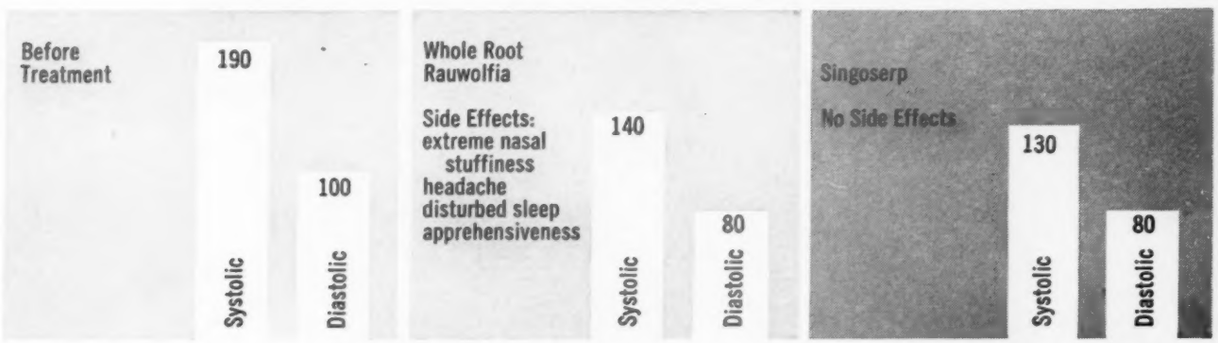
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Ambodryl® hydrochloride (bromodiphenhydramine hydrochloride, Parke-Davis)	24 mg.
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Dihydrocodeinone bitartrate	⅙ gr.
Ammonium chloride	8 gr.
Potassium guaiacolsulfonate	8 gr.
Menthol	q.s.
Alcohol	5%

Supplied: Bottles of 16 ounces and 1 gallon.

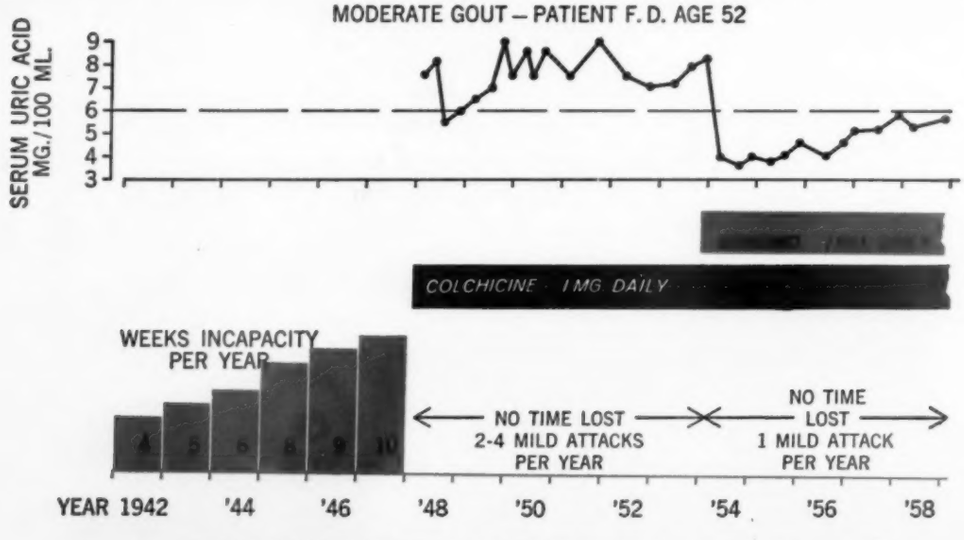
Dosage: Every three or four hours—adults, 1 to 2 teaspoonfuls; children ½ to 1 teaspoonful. 27160

◈ Exempt narcotic

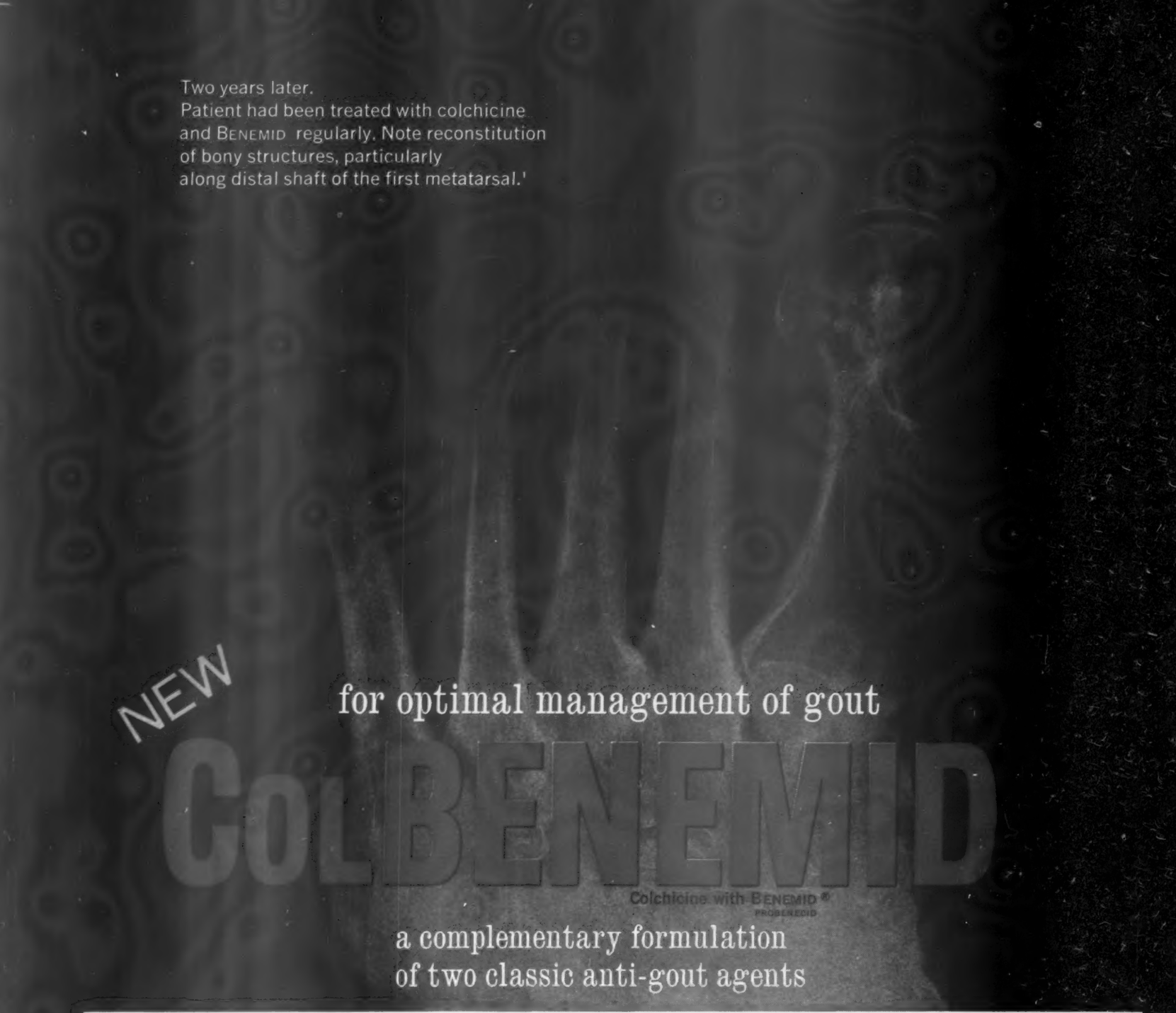
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Dosage between acute episodes: Mild, 1 tablet a day; moderate, 1 tablet twice daily; severe, 1 tablet three or more times daily.

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1. Talbott, J. H.: Gout, New York, Grune & Stratton, 1957, pp. 162, 163. 2. Talbott, J. H.: Gouty arthritis, Minn. Med. 42:1044, Aug. 1959. 3. Talbott, J. H.: Recognition and treatment of gouty arthritis, Current Medical Digest 26:57, Nov. 1959.

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Average Dose: Initial, 40-60 mg. For elderly and/or debilitated patients, 20-30 mg. *Maintenance*, 5-10 mg. daily, as indicated by prothrombin time determinations.

1. Baer, S., et al.: J.A.M.A. 167:704, June 7, 1958. 2. Moser, K. M.: Disease-a-Month, Chicago, Yr. Bk. Pub., Mar., 1960, p. 13.

*Manufactured under license from the Wisconsin Alumni Research Foundation.

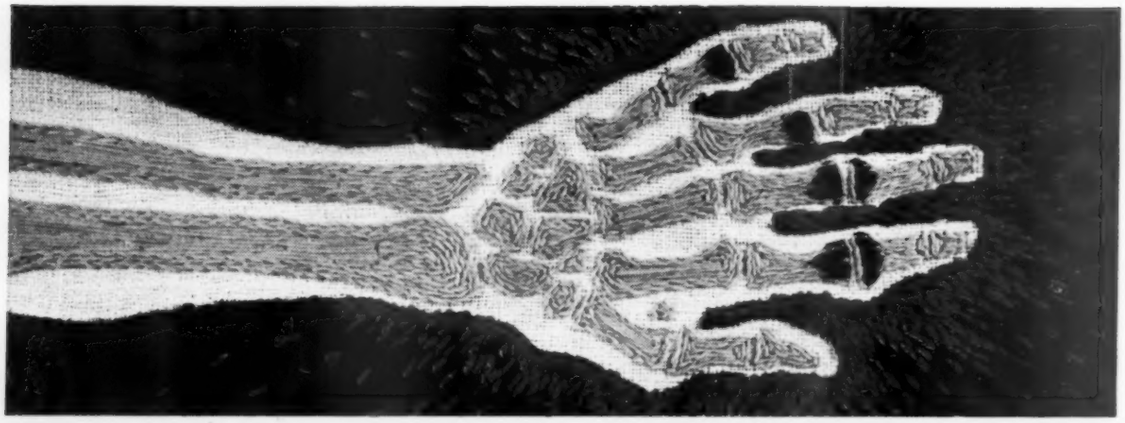
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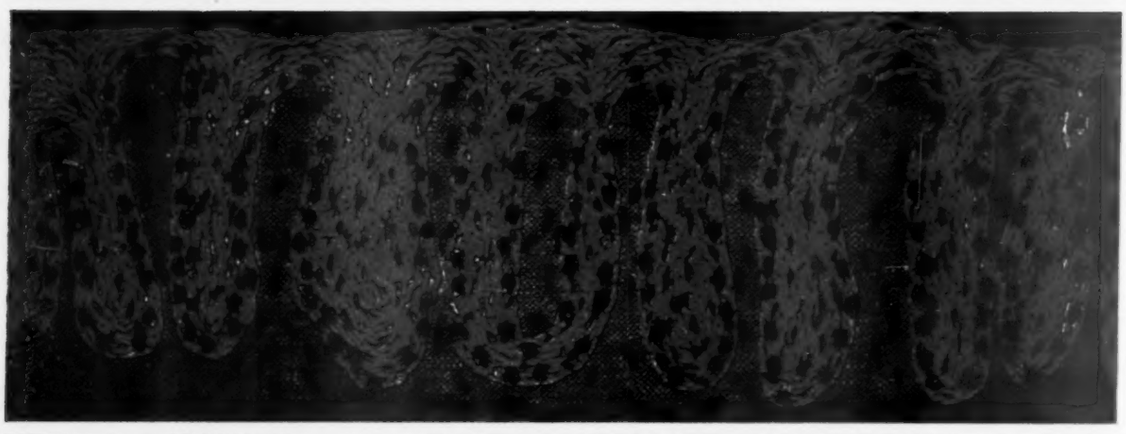
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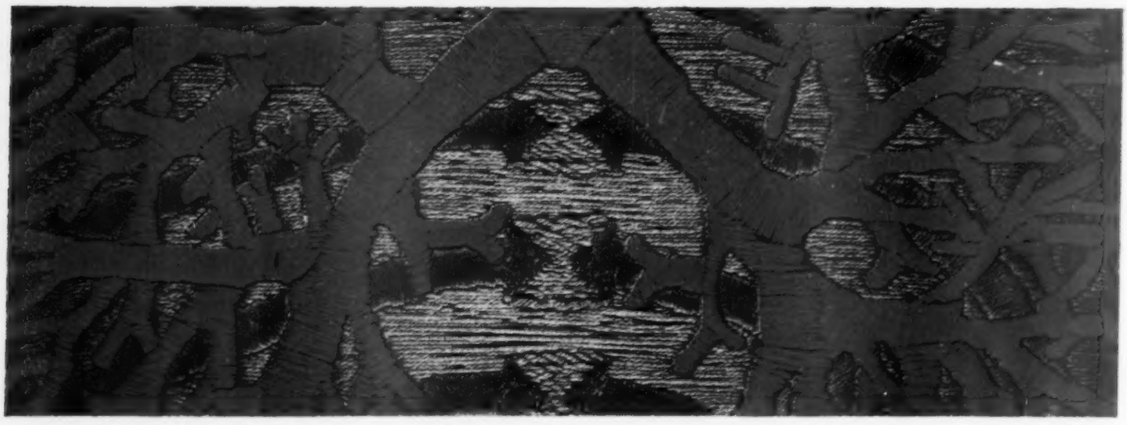
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***Fuchs, M.: A review of the thiazide pharmacology, Paper presented at Puerto Rican M. Soc., San Juan, Puerto Rico, Jan., 1960.**

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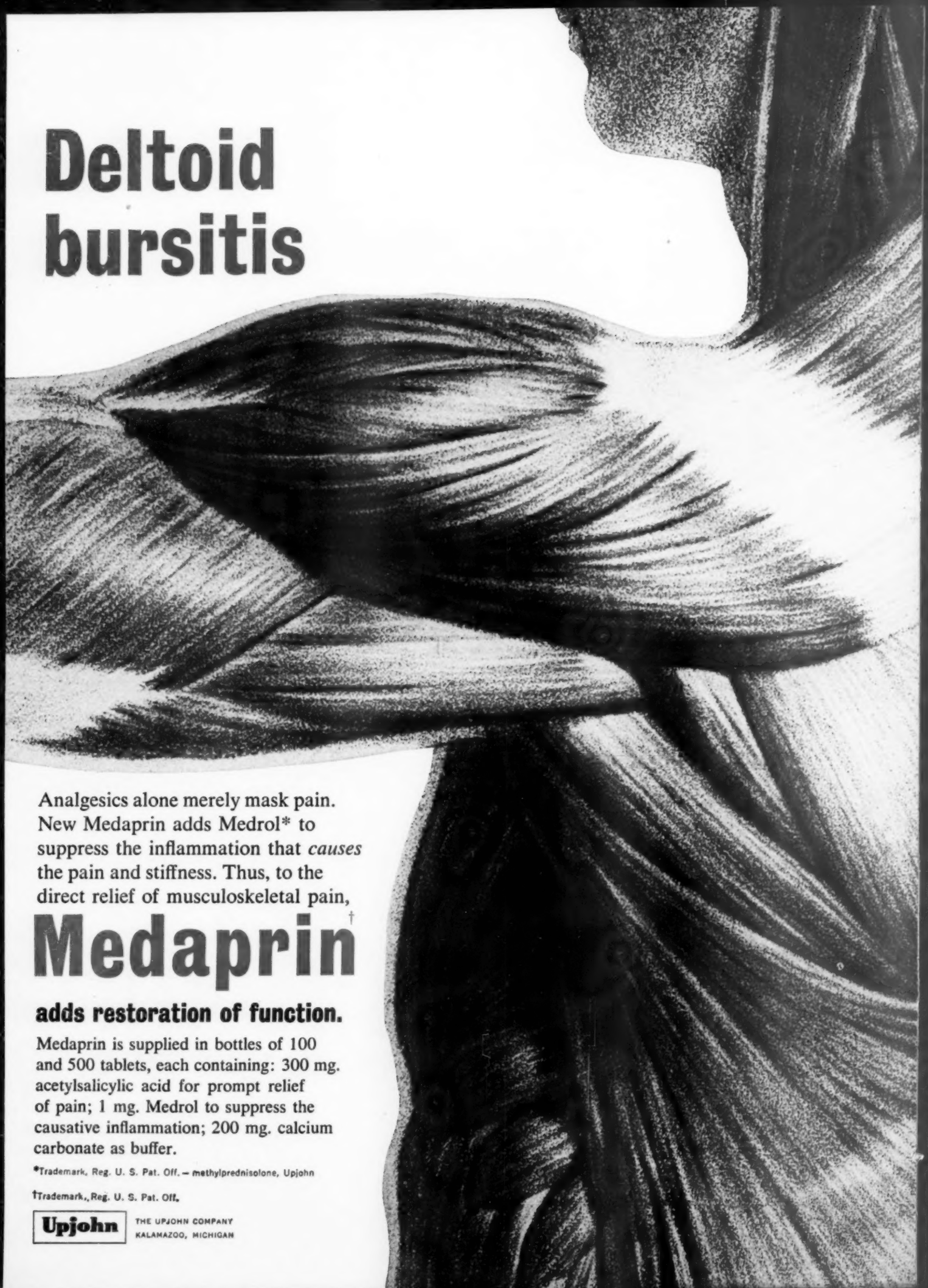
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". . . our program has been one of polypharmacy in which we attempt to deplete body sodium with chlorothiazide. This drug is continued indefinitely as background medication for all antihypertensive drugs." Moyer, J. H.: Am. J. Cardiology, **3**:199, (Feb.) 1959.



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in cirrhosis with ascites

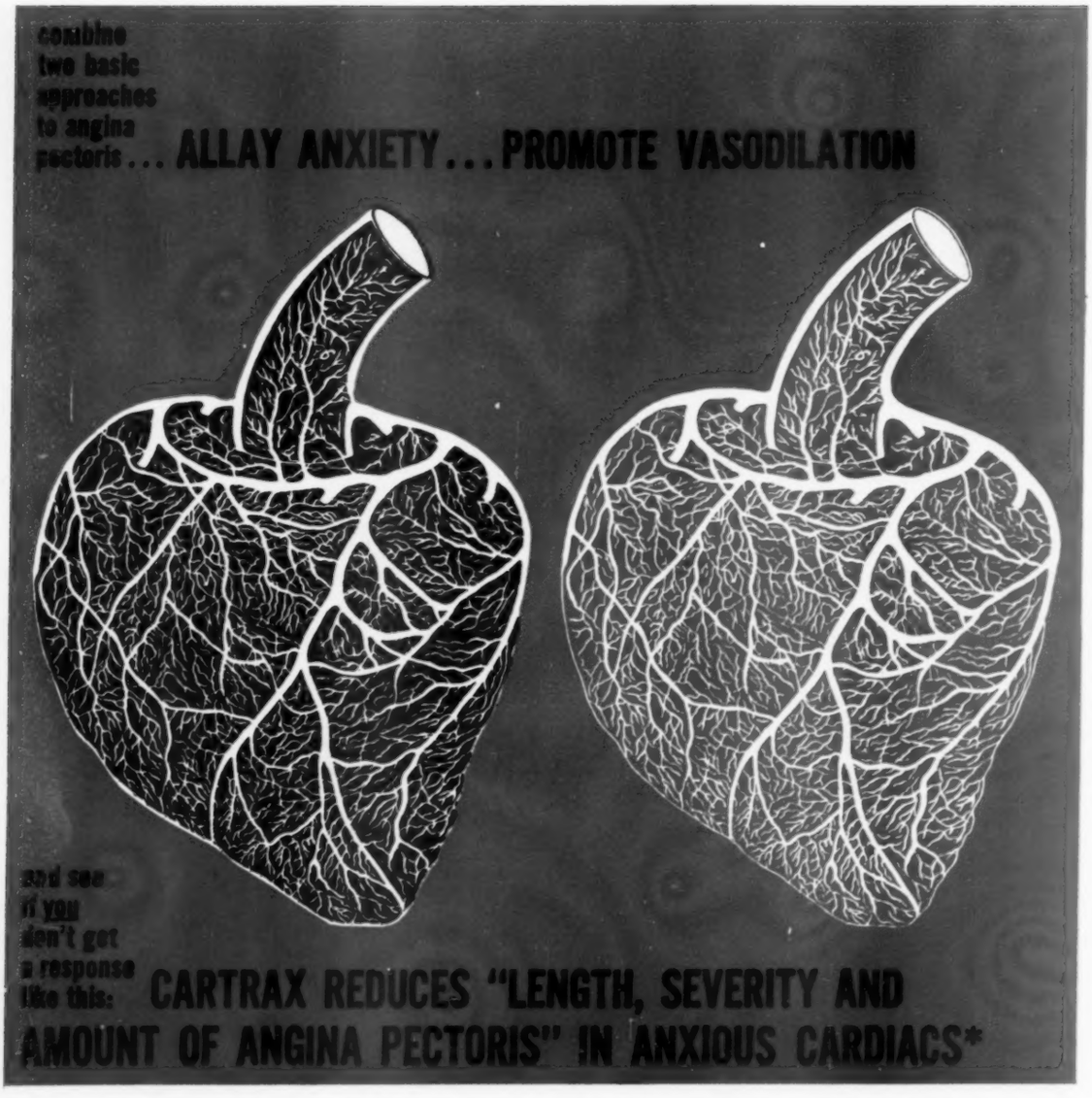
"All three of the patients with Laennec's cirrhosis, ascites and edema had a favorable response, with a mean weight loss of 8 lbs., during the five-day treatment period with a slight decrease in edema." Castle, C. N., Conrad, J. K. and Hecht, H. H.: Arch. Int. Med., **103**:415, (March) 1959.



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"In a study of 10 patients with the nephrotic syndrome associated with various types of renal disease, orally administered chlorothiazide was a successful, and sometimes dramatic, diuretic agent." Burch, G. E. and White, M. A., Jr.: Arch. Int. Med., **103**:369, (March) 1959.

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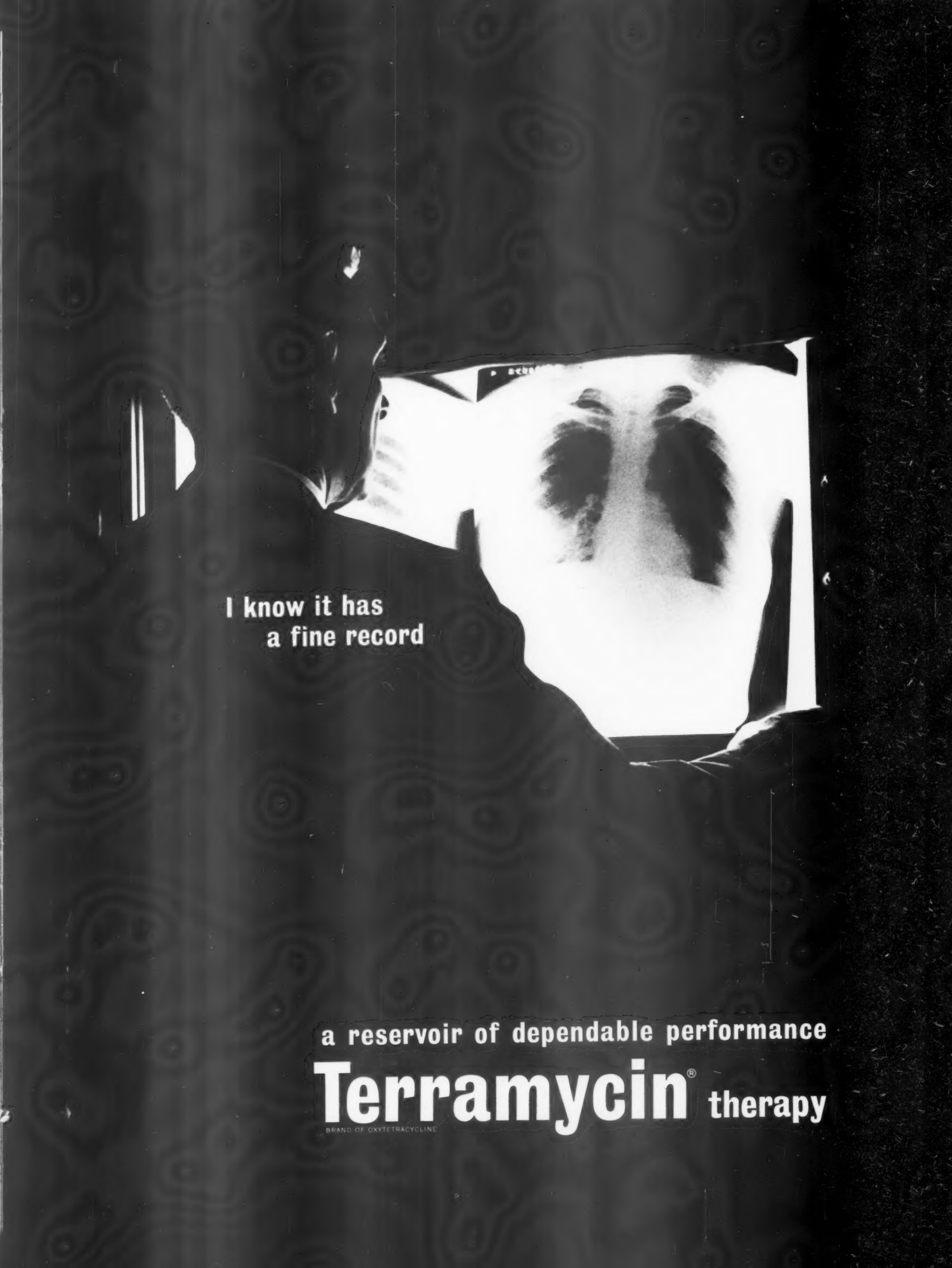
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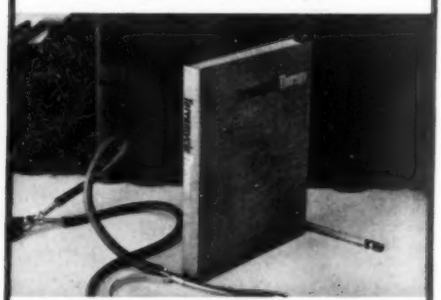
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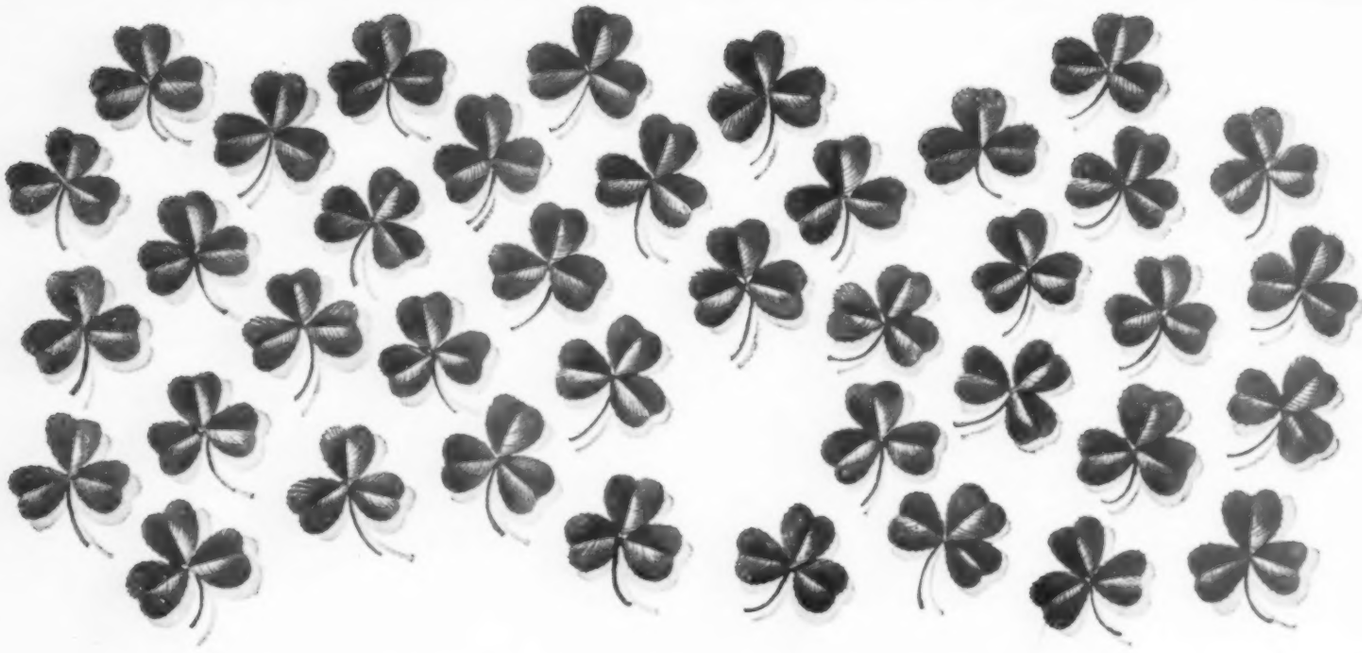
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*David, N. A.; Logan, N. D., and Porter, G. A.: Evaluation of Thioridazine (Mellaril), a New Phenothiazine, in The Hospitalized Patient, A. M. & C. T 7:364 (June) 1960.



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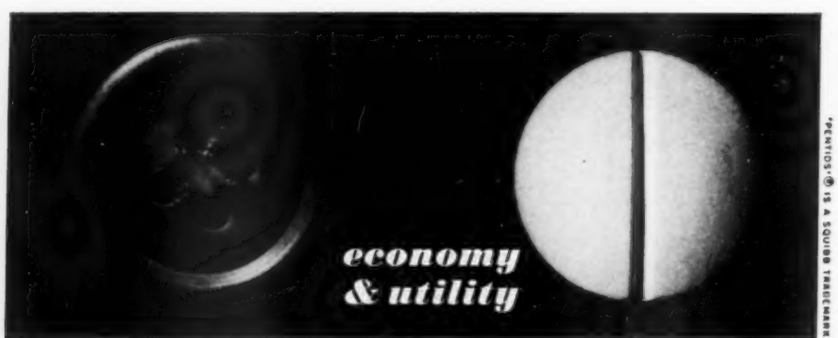
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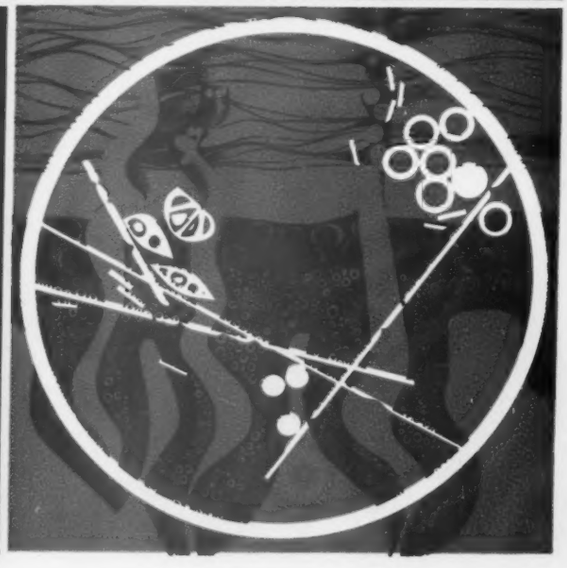
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(1) Fox, H. H.: Antibiot. Med. & Clin. Therapy *6*:85, 1959.
(2) Lubowe, I. I.: Antibiot. Med. & Clin. Therapy *4*:81, 1957.
(3) Murphy, J. C.: Rocky Mountain M. J. *55*:53 (June) 1958.
(4) Pace, B. F.: Med. Rec. & Ann. *51*:370, 1957.

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safe and practical treatment of the postcoronary patient

A basic characteristic of the postcoronary patient, whether or not cholesterol levels are elevated, is his inability to clear fat from his blood stream as rapidly as the normal subject.[1-3] *Figure #1* graphically illustrates this difference in fat-clearing time by comparing atherosclerotic and normal subjects after a fat meal.[3]

"Slow clearers" gradually accumulate an excess of fat in the blood stream over a period of years as each meal adds an additional burden to an already fat-laden serum. As shown in *figure #2,* the blood literally becomes saturated with large fat particles, presenting a dual hazard to the atherosclerotic patient: the long-term danger of deposition of these fats on the vessel walls,[4] and the more immediate risk of high blood fat levels after a particularly heavy meal possibly precipitating acute coronary embarrassment.[5]

In *figure #3,* the test tube at the left contains lipemic serum, while the one at the right contains clear, or normal serum. If serum examined after a 12-hour fasting period presents a milky appearance, this is a strong indication that the patient clears fat slowly and is a candidate for antilipemic therapy in an effort to check a potentially serious situation.

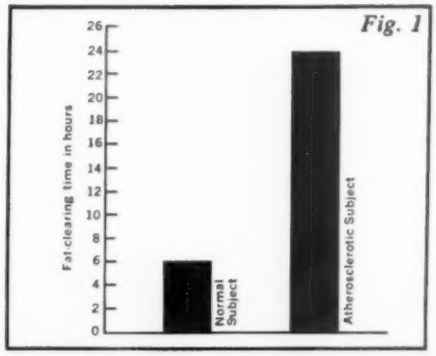
'Clarin', which is heparin in the form of a *sublingual tablet,* has been demonstrated to clear lipemic serum.[2,6,7] Furthermore, a two-year study using matched controls resulted in a statistically significant reduction of recurrent myocardial infarction in 130 patients treated with 'Clarin'.[8]

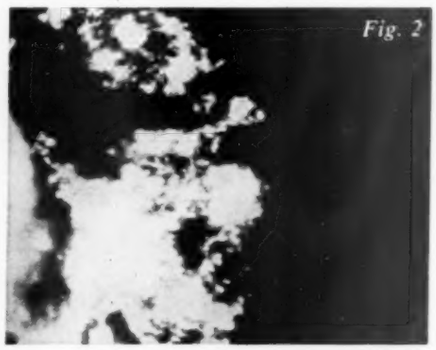
'Clarin' therapy is simple and safe, requiring no clotting-time or prothrombin determinations. Complete literature is available to physicians upon request.

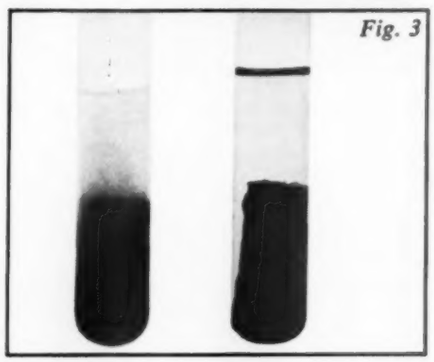
References: **1.** Anfinsen, C. B.: Symposium on Atherosclerosis, National Academy of Sciences, National Research Council Publication 338, 1955, p. 218. **2.** Berkowitz, D.; Likoff, W., and Spitzer, J. J.: Clin. Res. *7*:225 (Apr.) 1959. **3.** Stutman, L. J., and George, M.: Clin. Res. *7*:225 (Apr.) 1959. **4.** Wilkinson, C. F., Jr.: Annals of Int. Med. *45*:674 (Oct.) 1956. **5.** Kuo, P. T., and Joyner, C. R., Jr.: J.A.M.A. *163*:727 (March 2) 1957. **6.** Fuller, H. L.: Angiology *9*:311 (Oct.) 1958. **7.** Shaftel, H. E., and Selman, D.: Angiology *10*:131 (June) 1959. **8.** Fuller, H. L.: Circulation *20*:699 (Oct.) 1959.

Clarin*

(sublingual heparin potassium, Leeming)







Indication: For the management of hyperlipemia associated with atherosclerosis, especially in the postcoronary patient.

Dosage: After each meal, hold one tablet under the tongue until dissolved.

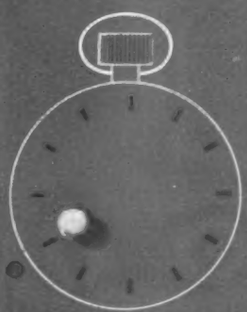
Supplied: 'Clarin' is supplied in bottles of 50 pink, sublingual tablets, each containing 1500 I.U. of heparin potassium.

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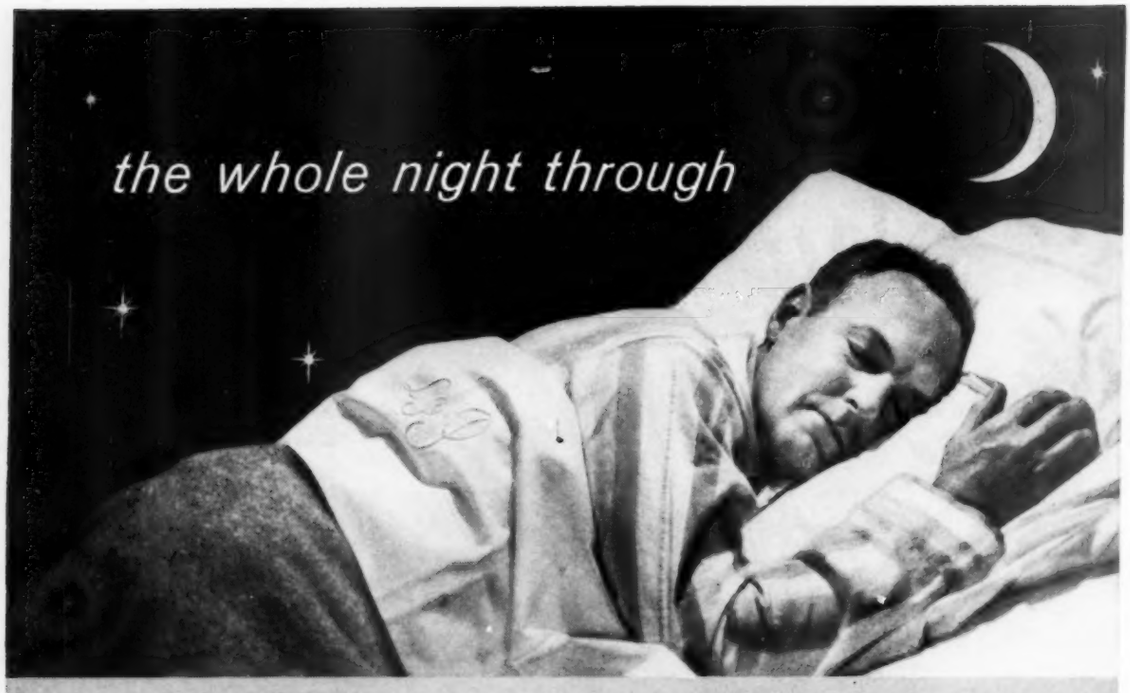
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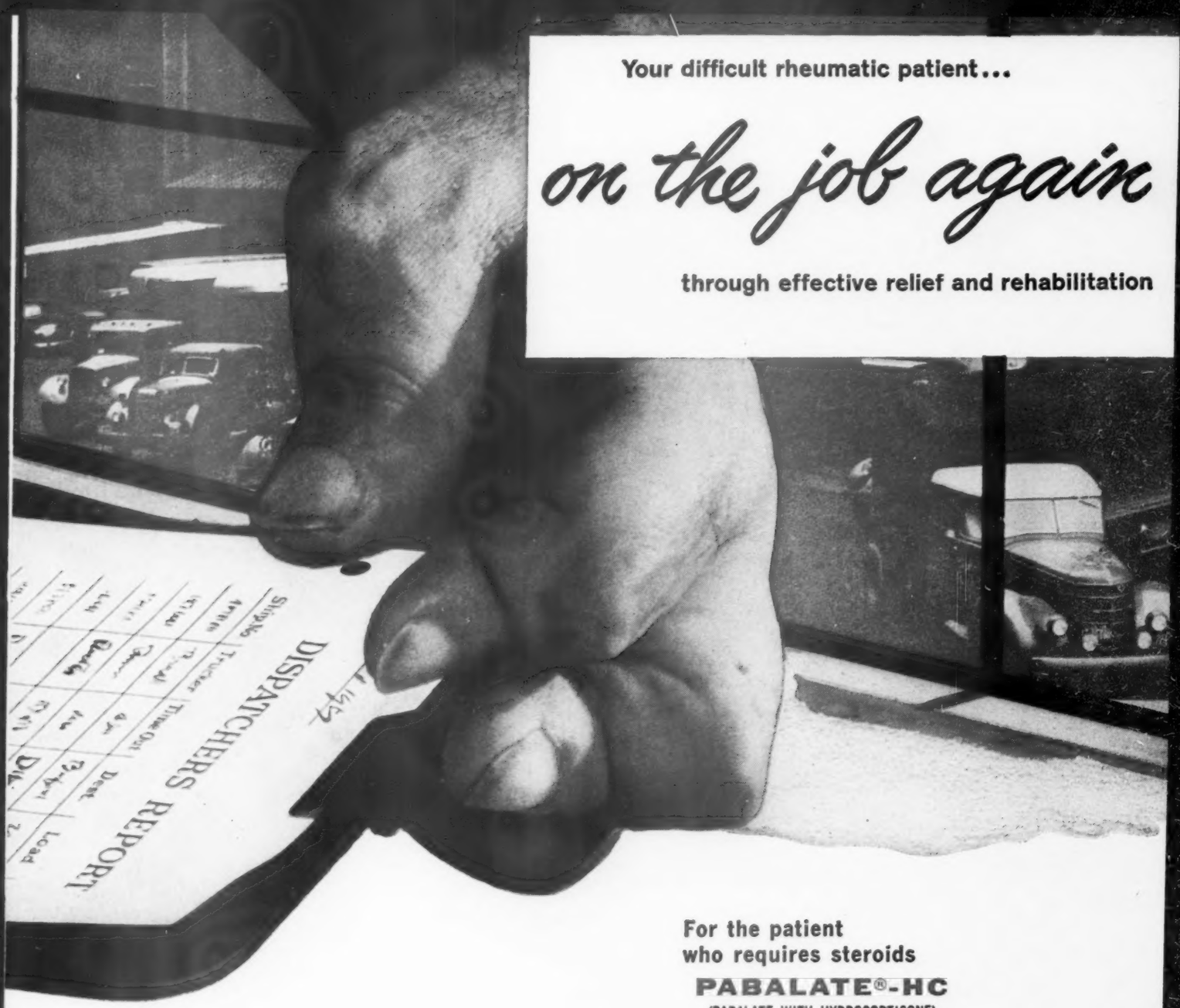
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1. Bellet, S., Finkelstein, D., and Gilmore, H.: A.M.A. Arch. Int. Med. 100:750, 1957.
2. Bellet, S.: Amer. Heart J. 56:479, 1958.
3. Finkelstein, D.: Penn. Med. J. 61:1216, 1958.
4. Bellet, S.: Amer. J. Cardiology 4:268, 1959.

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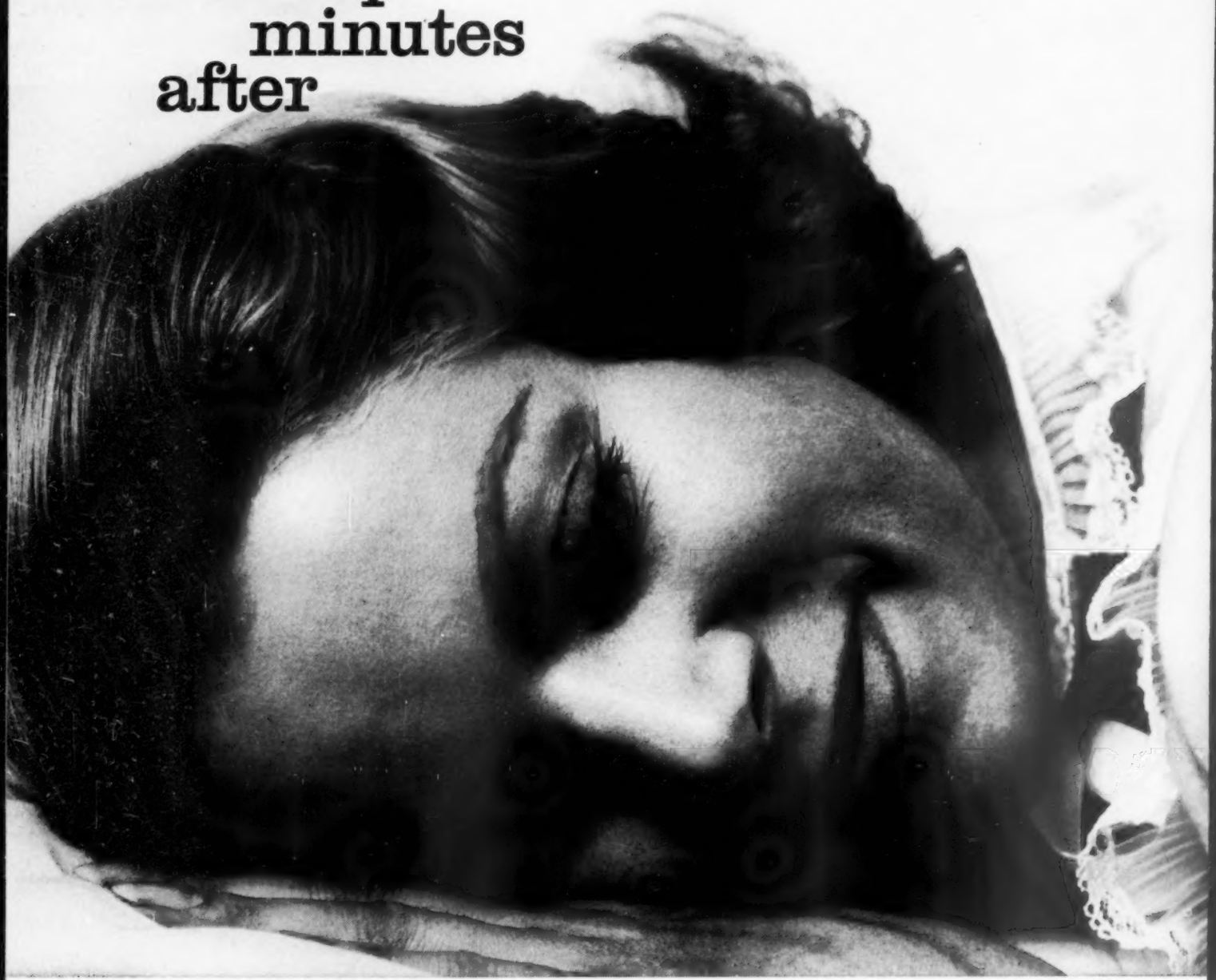
Hydrocortisone (alcohol) ..... 2.5 mg.
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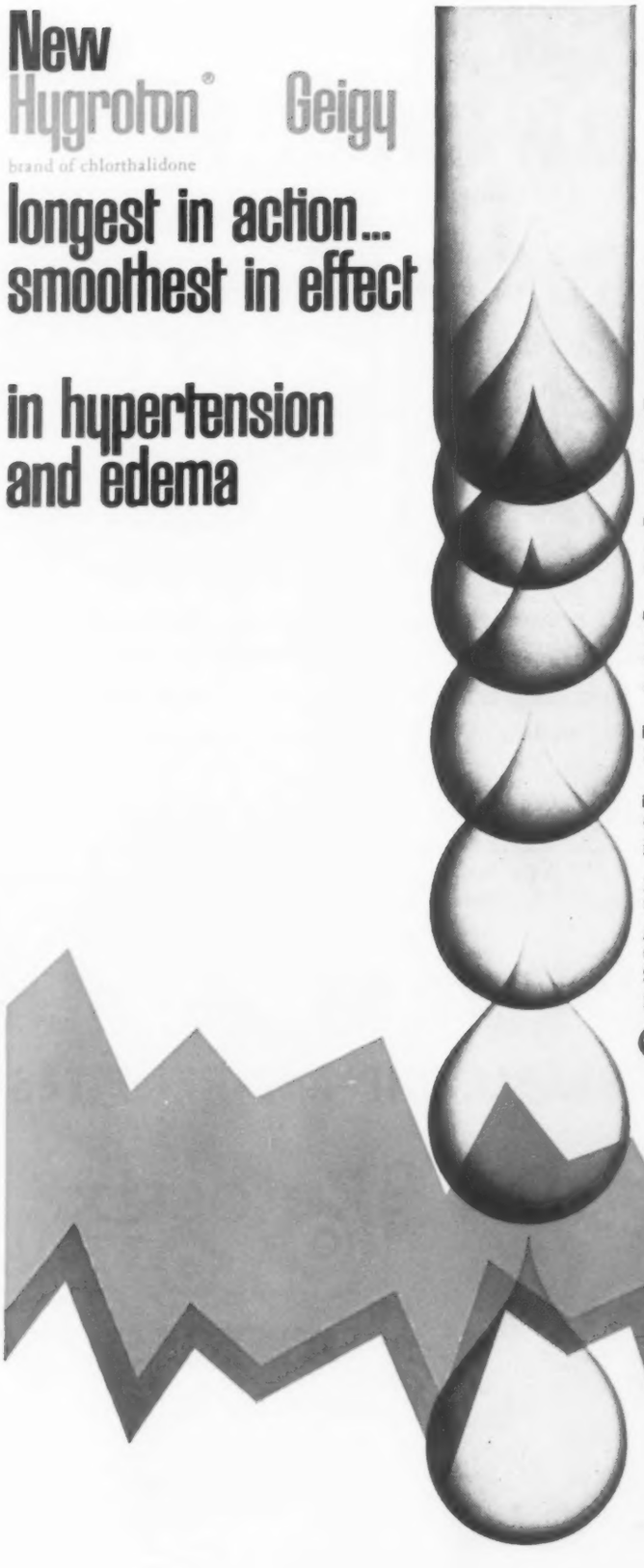
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References:
(1) Stenger, E. G., et al.: Schweiz. med. Wchnschr. 89:1126, 1959. (2) Fuchs, M., Res: et al.: Current Therap. Research 2:11, January, 1960. (3) Ford, R. V.: Manuscript submitted for publication.

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REFERENCES: (1) Wells, B. B.: Clinical Pathology: Application and Interpretation, ed. 2, Philadelphia, Saunders, 1956, p. 233. (2) Duncan, G. G.: Diseases of Metabolism: Detailed Methods of Diagnosis and Treatment, ed. 4, Philadelphia, Saunders, 1959, p. 795. (3) Williamson, P.: Practical Use of the Office Laboratory and X-ray, Including the Electrocardiograph, St. Louis, Mosby, 1957, p. 41. (4) Mehlman, J. S.; Zitman, I. H., and Platt, S. S.: M. Clin. North America 43:615 (March) 1959.

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THE PRESENT STATUS OF ORAL PENICILLIN

1
2
3
4
5
6



A Comparison of Potassium Penicillin V and Synthetic Penicillin

1 *On antibacterial activity in the serum*

In a recent study, Griffith[1] undertook to compare the antibacterial activity of three oral penicillins.

Included were forms of potassium penicillin V and G and alpha-phenoxyethyl penicillin. Typical crossover procedures were used, and results were measured by the tube dilution technique.

When potassium penicillin V was compared directly with the synthetic form, Griffith found that the former not only produced peak levels of activity faster, but in values almost half again as high as those registered with the synthetic. He wrote: "Measuring antibacterial activity in the sera using the serial tube dilution method and a pathogen as the indicator organism is more informative regarding relative antibacterial effectiveness than reporting 'blood levels' in micrograms."

2 *Greater activity of potassium penicillin V confirmed*

A direct laboratory comparison[2] of the two penicillins revealed a measurable difference in antibacterial activity. In the following chart, these values are interpreted in terms of reciprocal of the dilution inhibiting growth.

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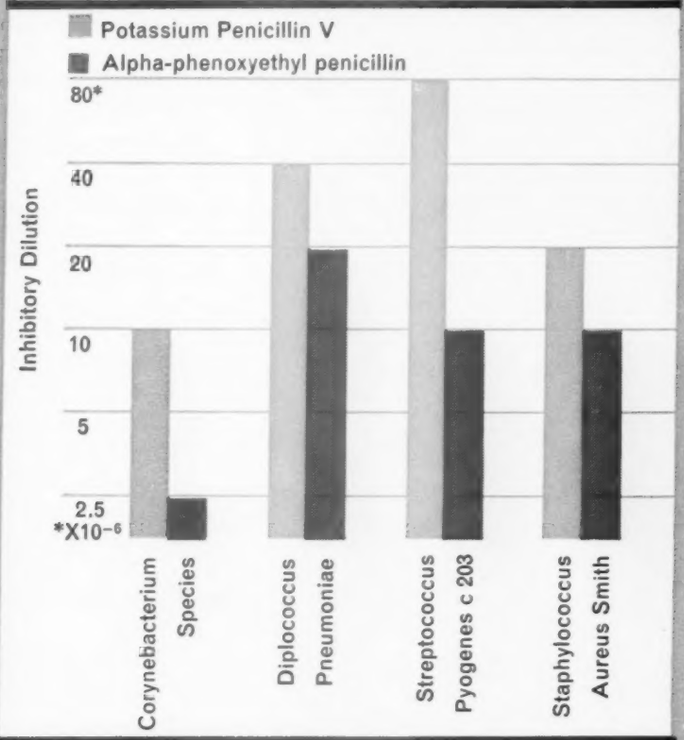
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(Potassium Penicillin V)

offers greater antibacterial activity
against penicillin-sensitive organisms

In Vitro Activity of Penicillin V and Alpha-Phenoxyethyl Penicillin

Note, that against four strains of disease-producing organisms, potassium penicillin V gives from two to eight times more antibacterial activity than alpha-phenoxyethyl penicillin.



3 *On high blood levels*

A number of investigators have demonstrated serum concentrations in the same range following equivalent doses of potassium penicillin V and alpha-phenoxyethyl penicillin.

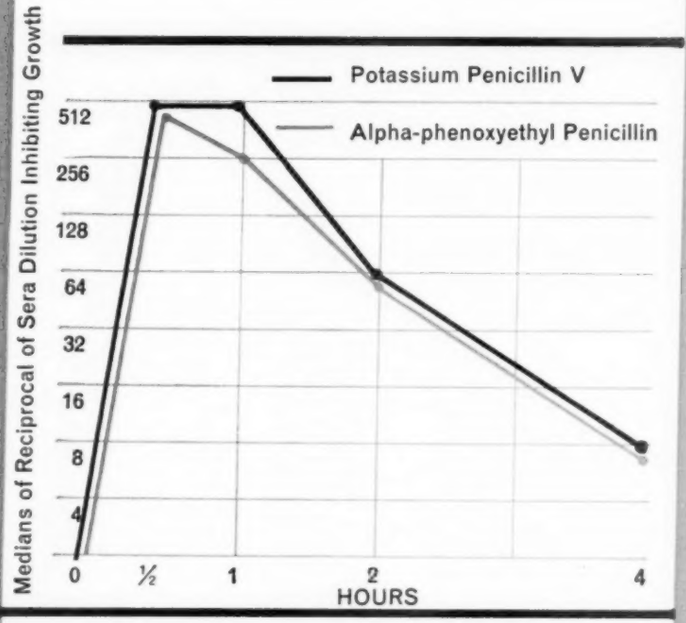
McCarthy, et al.,[3] after investigating the two penicillins, reported: "These crossover studies indicate that the new synthetic penicillin and penicillin V are absorbed in a remarkably similar manner and degree and that these forms of penicillin yield quite comparable serum levels when given in the same manner to the same individuals at different times."

At Abbott Laboratories, scientists[2] found after their study that antibacterial activity in the sera of human subjects given equivalent doses of penicillin V or synthetic penicillin showed no significant differences between the two penicillins.

Comparative Serum Antibacterial Activity Study of Potassium Penicillin V and Alpha-phenoxyethyl Penicillin

Doses of 250 mg. (400,000 units) were given to 30 human subjects. The study revealed little difference in serum antibacterial activity between the two penicillins.

The antibacterial activity of the sera was determined by a tube dilution procedure employing *Streptococcus pyogenes* C203[3].



In England, where synthetic penicillin was first discovered and marketed, the Journal of the British Medical Association (after studying a commercial brochure) stated: "There is no evidence here of any activity superior to that of other penicillins against Gram-negative species, and what differences there are against sensitive species are in favour of penicillin G or V or both; this applies to all varieties of streptococci tested.[4]"

4 *On resistance to penicillinase*

In comment on this phase of the new penicillin, McCarthy et al. stated[3]: "Both of these penicillins are qualitatively similar to penicillin G in their susceptibility to penicillinase produced by *Staphylococcus aureus.*"

In further comment on this problem, they said: "Other observations not detailed here have indicated some differences in susceptibility of a number of strains of staphylococci to these 2 forms of penicillin and to penicillin G, but these differences, too, are not large enough to be of clinical importance..."

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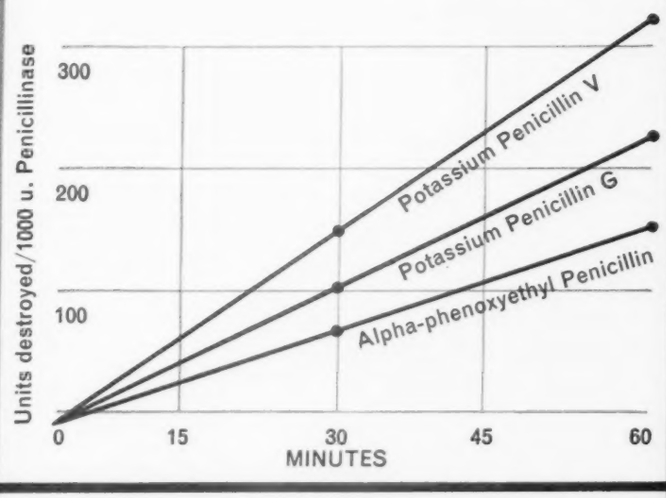
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offers greater antibacterial activity
against penicillin-sensitive organisms

At Abbott, investigators studying the same subject[2] found that synthetic penicillin is destroyed by penicillinase at a rate approximately ⅔ that of penicillin G and ½ that of penicillin V.

Sensitivity to Penicillinase

Note that the rate of destruction of all three penicillins is so great that the differences have no therapeutic significance.



Additional studies by the same scientists[2] indicated that both synthetic penicillin and penicillin V were relatively inactive against several penicillinase-producing staphylococci. (See chart below).

Comparative Activity of Potassium Penicillin V and Alpha-phenoxyethyl Penicillin Against Penicillinase-Producing Staphylococci

Note that although synthetic penicillin is slightly more active, the concentration required to inhibit growth is greatly in excess of an obtainable therapeutic level, and therefore of little therapeutic significance.

Strain	M.I.C., mcg./ml. Penicillin V	Synthetic Penicillin
Wise J155	> 800	> 800
Wise J306	300	75
W. E. B.	> 800	> 800
Wise J628	> 400	> 400
Treaster	> 800	800
Gill 1322	> 800	> 800

COMPOCILLIN®-VK

(Potassium Penicillin V)

offers greater antibacterial activity
against penicillin-sensitive organisms

5 *On the comparative safety of oral penicillin*

In 1957, a nationwide survey[5] of antibiotic reactions was made. One of the conclusions reached by the investigators in regard to penicillin reactions was, "It is clear also that the oral route is the much safer method of administration, both from the standpoint of numbers of reactions and of mortality." There is no evidence to show that any form of oral penicillin is less allergenic than another oral form.

6 *On the advantages of Compocillin-VK*

Compocillin-VK (potassium penicillin V) offers early, high concentrations of antibacterial activity against penicillin-sensitive organisms. Initial activity levels are higher than those obtained with intramuscular penicillin G. And normally, patients respond just as well as with the injectable.

Additionally, Compocillin-VK (potassium penicillin V) offers an easy-to-take form for every patient—any age. It comes in tiny Filmtabs®, 125 mg. (200,000 units) and 250 mg. (400,000 units). And in Granules for Oral Solution. When reconstituted, each tasty 5-ml. teaspoonful provides a fresh, cherry-flavored solution containing 125 mg. of potassium penicillin V.

1. Griffith, R. S., Comparison of Antibiotic Activity in Sera after the Administration of Three Different Penicillins, Antibiot. Med. & Clinical Therapy, 7:2, Feb., 1960.
2. Unpublished Data, Microbiology Department, Abbott Laboratories.
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5. Welch, H., Lewis, C. N., Weinstein, H. I., Boeckman, B. B., Severe Reactions to Antibiotics—A Nationwide Survey, Antibiotics Annual 1957-58.

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In mild to moderate hypertension, Serpasil is basic therapy, effective alone "... in about 70 per cent of cases..."*

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In all grades of hypertension, Serpasil may be used as a background agent. By permitting lower dosage of more potent antihypertensives, Serpasil minimizes the incidence and severity of their side effects.

CIBA
SUMMIT, N. J.

*Coan, J. P., McAlpine, J. C., and Boone, J. A.: J. South Carolina M. A. 51:417 (Dec.) 1955.

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(1) Yu, T. F., Burns, J. J., and Gutman, A. B.: Arch. & Rheumat. 5:532, 1958. (2) Kersley, G. D.; Cook, E. R., and Tovey, D. C. J.: Ann. Rheumat. Dis. 17:328, 1958. (3) Ogryzlo, M. A., and Harrison, J.: Ann. Rheumat. Dis. 16:423, 1957.

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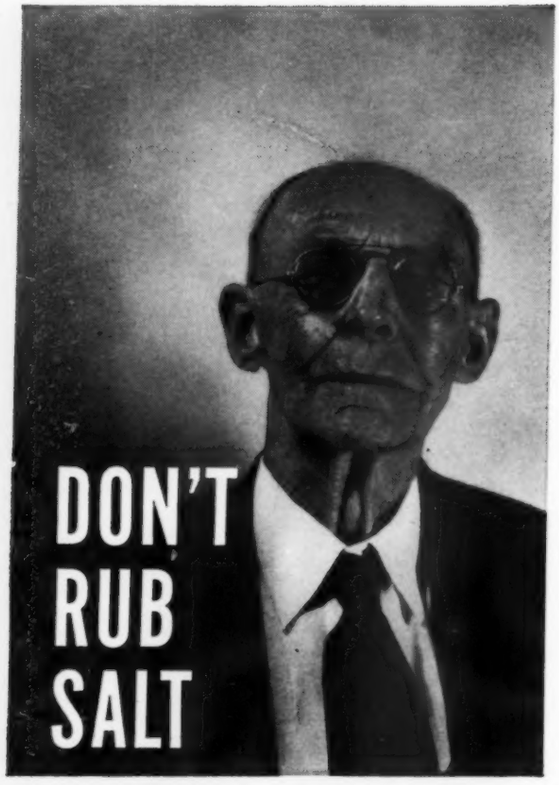
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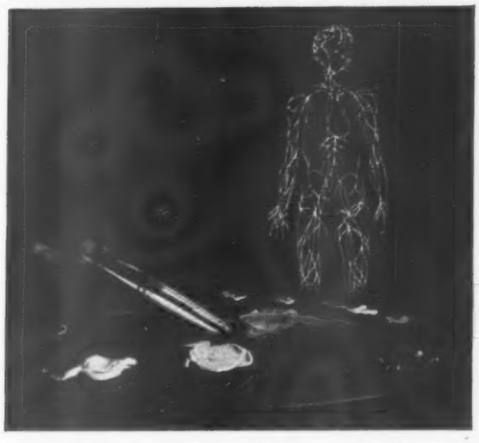
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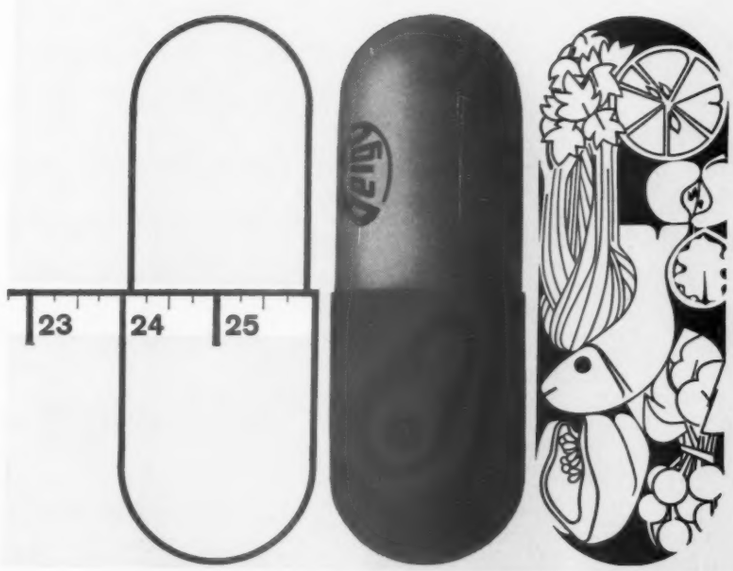
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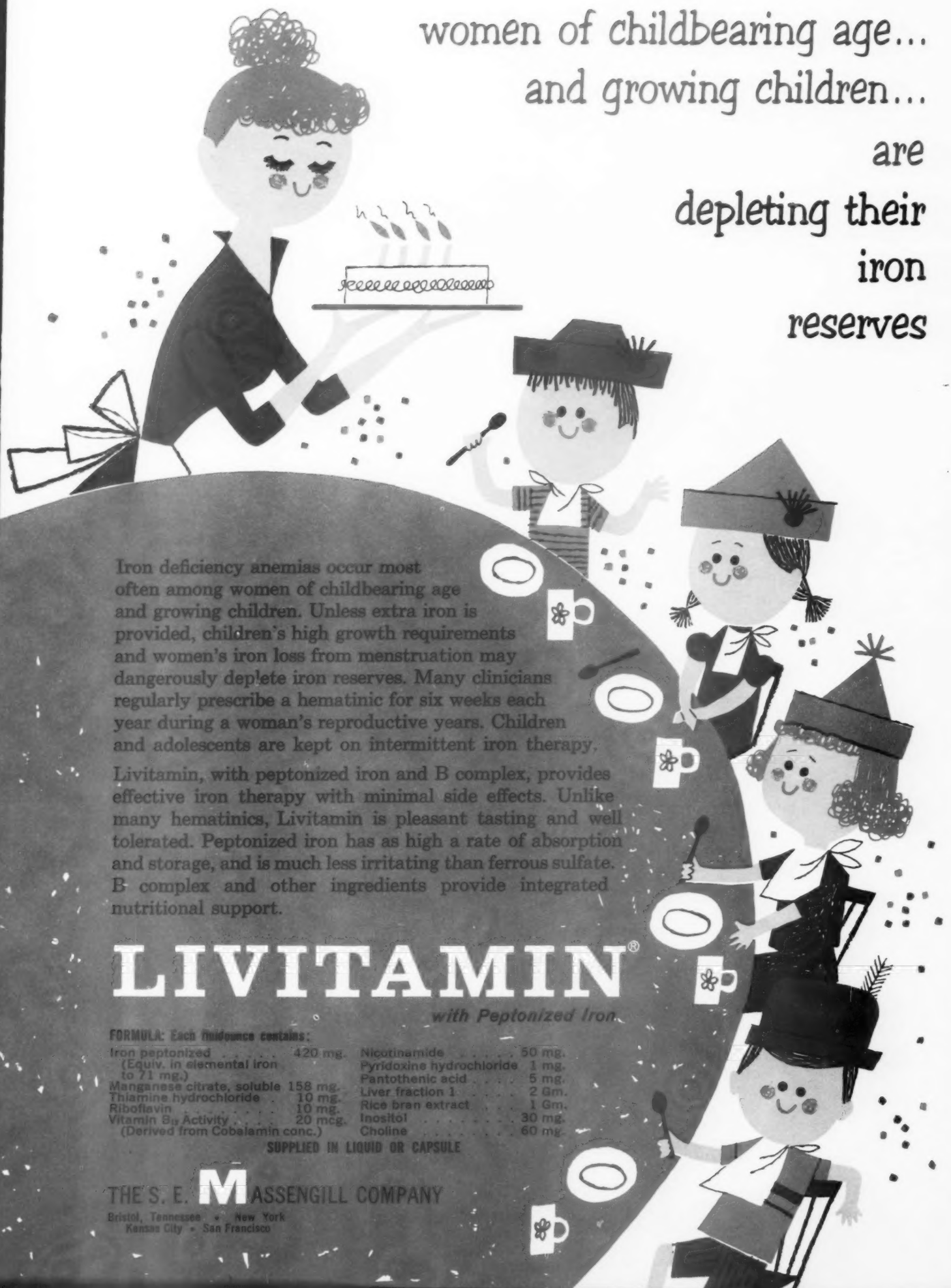
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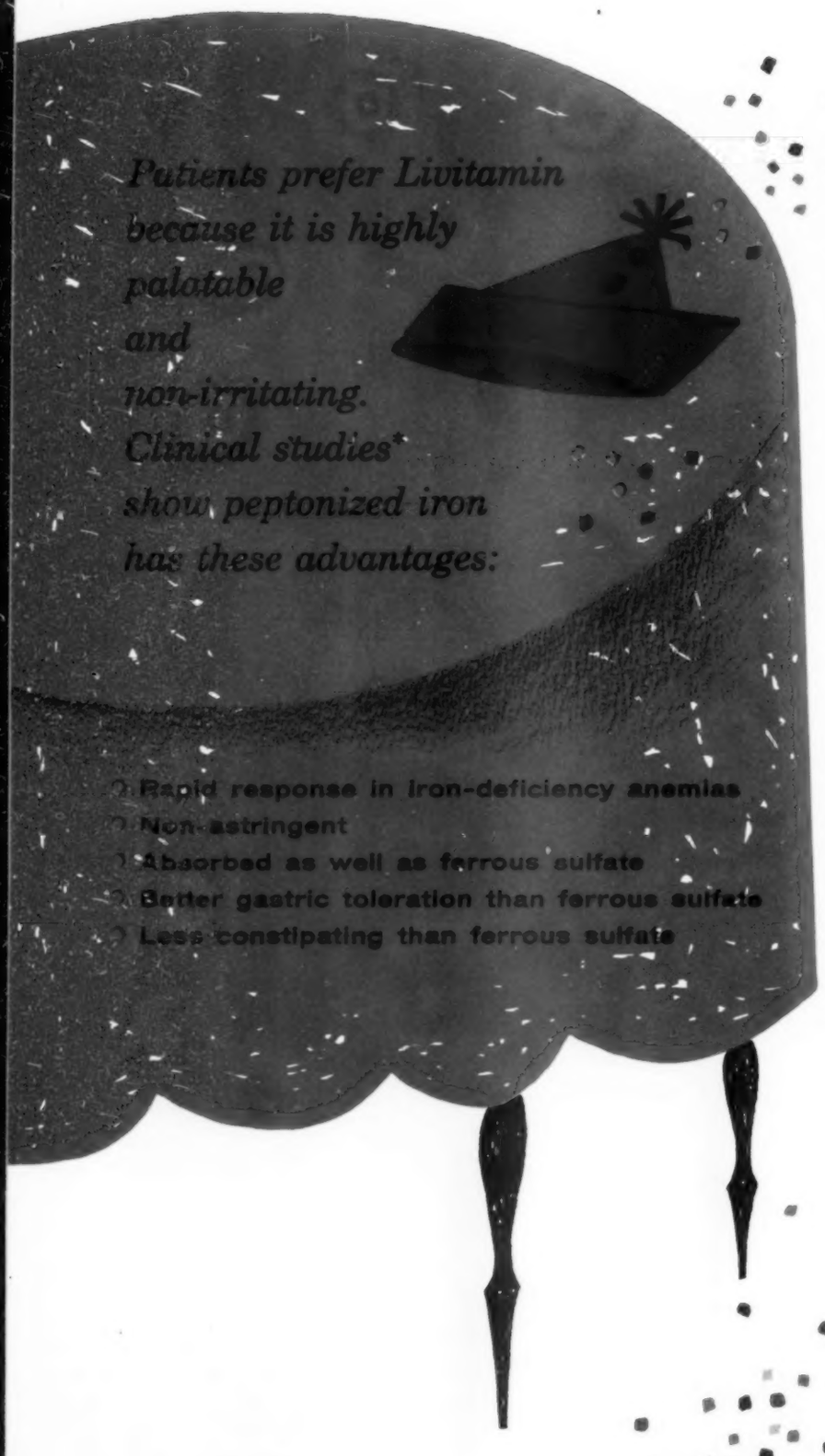
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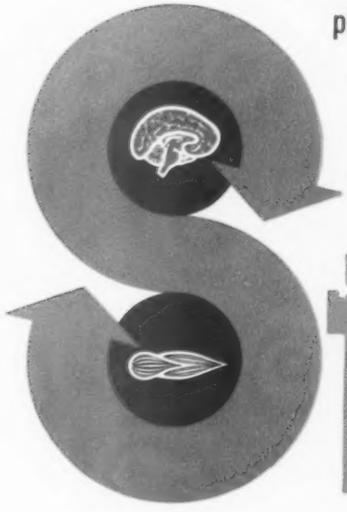
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The American Journal of Medicine

VOL. XXIX SEPTEMBER 1960 NO. 3

Editorial

Current Status of Steroid Therapy in Chronic Glomerulonephritis in the Adult

The Unnatural History of Bright's Disease

TODAY the internist is increasingly faced with a problem hitherto chiefly the pediatrician's: whether to treat certain types of Bright's disease with adrenal corticosteroids. At least three considerations are involved: (1) What therapeutic result can be expected in a particular patient's form and stage? (2) How significantly does the result differ from expectations were the disease to proceed in its natural history unmolested; specifically, are complications incurred by treatment worth any gains, measured not simply in life span but also in daily function? (3) If the decision is to treat; with what, how much, how continuously, how long?

The published records of the recent annual conferences [*1*] on the nephrotic syndrome present vivid year by year accounts of our pediatric colleagues' struggles with these matters. Why these have fallen to the pediatrician's lot with (until recently) but an occasional assist from the internist emerges from a brief historical consideration.

SOME HISTORY, NOT TOO ANCIENT

With the first glowing reports [*2*] of ACTH, then of cortisone, in inflammations ranging in etiology from well known microorganisms (e.g., the pneumococcus) to mechanisms of which our knowledge is still fragmentary, trial in glomerulonephritis was not long delayed. The first small series reported in the American literature came from an internist [*3*]. By including an age range from three to thirty-seven years, she made no distinction between childhood and adult responsiveness. This and subsequent early reports were notably sparse in evidence for the prompt anti-inflammatory effects in glomerulonephritis comparable to those in "allergic" syndromes (e.g., uveitis, bronchial asthma, atopic dermatitis) or inflammations of unknown etiology (e.g., rheumatoid arthritis, gout). Rather, these reports emphasized promotion of diuresis of salt and water at a stage of Bright's disease which is minimally inflammatory to the histopathologist and which has been called "the degenerative stage" by some of its most dedicated clinical students [*4*].

Particularly in children, reports from many centers agreed that, following one or more short courses, diminution or transient abolition of proteinuria and hyperlipemia, restoration of serum albumin and gamma globulin levels, and above all, substantial diuresis occurred with sufficient regularity to make ACTH and cortisone useful additions to an often bare therapeutic armamentarium against the recalcitrant anasarca of some patients with nephrosis. The observations by the Cleveland group [*5*] are representative of many careful studies in the first half of the 1950's: (1) they achieved diuresis in some 80 per cent of children treated; (2) they noted a poorer prognosis in

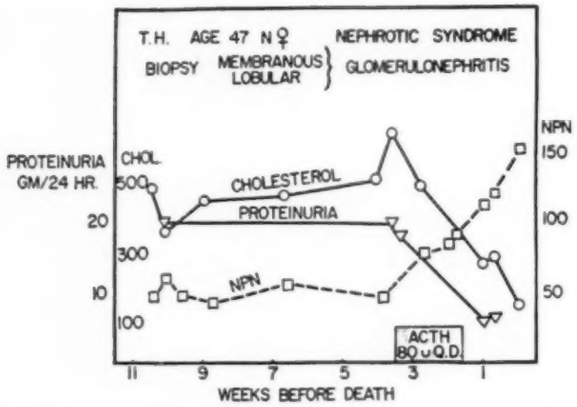


FIG. 1. The precipitous "cruciate" biochemical course of a forty-seven year old Negro woman whose diagnosis of chronic membranous glomerulonephritis was made by biopsy one week before, and autopsy ten days after the end of the indicated course of ACTH. The ACTH was aimed at the relief of intractable anasarca which had appeared insidiously fourteen months before. The chief histological difference between biopsy and autopsy of the kidneys lay in accentuated afferent arteriolar necrosis in the latter. (We are indebted to Dr. P. D. Szanto, Director of Pathology, Cook County Hospital, for guidance in histopathologic interpretation.)

diuretic failures than in successes; (3) they emphasized that successful diuresis was no guarantee of ultimate cure; in many instances transitory diuresis was followed sooner or later by progression toward a uremic death (the fate of about one-third of the children with the nephrotic syndrome).

Despite an enthusiastic start, the contemporaneous use of ACTH and cortisone in adult Bright's disease did not keep pace with use in children. Reasons of varying cogency may be cited:

(1) Beneficient influence in stages of the disease which are patently inflammatory was unimpressive. While clear-cut *decreases* in glomerular permeability to molecules the size of albumin has subsequently been demonstrated by refined technics [*6*], early workers with short courses encountered sporadic *increases* in proteinuria. When Bjørneboe [*7*] in Scandinavia wrote, "it is doubtful whether any permanent effect is obtained," and Thorn's group [*8*] in Boston listed glomerulonephritis in a table of diseases in which ACTH and cortisone are of "questionable value"; when, from the laboratory, evidence for efficacy in experimental renal inflammations was at best lukewarm,* at worst, downright deleterious; we suspect a good many workers with the adult disease deemed it unnecessary to bring their own equivocal and downright unhappy results to detailed publication.*

(2) Even in the waterlogged nephrotic subject, accumulating experience in many centers began to indicate (with one or two exceptions) that significant diureses occurred less often and less completely in the adult than in the child. In this hospital (with a 65 per cent Negro population) our own experience with short-term ACTH and cortisone as nephrotic diuretics seemed not only more discouraging than that reported elsewhere, but even dangerous by reason of sporadic but appreciable coincidence of apparently accelerated transition from the nephrotic to the dry uremic state.

THE "CRUCIATE COURSE"

This transition, well recognized by older students of nephritis, is ordinarily not abrupt. Of this "cruel paradox . . . a release and deliverance from the only symptom that has troubled them: their edema," Addis' classic description notes, "Change comes so quietly, we cannot tell when it begins." [*14*]

Figure 1 illustrates the course of an adult with nephrosis in whom both beginning and ending of a change is readily apparent, and for whom the renal histologic status shortly before and immediately after ACTH therapy was documented, respectively, by biopsy and necropsy. Named by our residents "the cruciate course" because of the crossing of the plots of non-protein nitrogen, proteinuria and lipemia, clinical encounters with this catastrophe may be gleaned from the pediatric

* The range reported in experimental renal disease can be thus illustrated: (1) Loeb and Seegal, and co-workers [*9*], showed that exhibition of the synthetic mineralocorticoid desoxycorticosterone aggravated the course and greatly accentuated the lesions of classical Masugi nephritis. (2) Rich and his group noted [*10*] differentiation in effects of cortisone and ACTH on glomerular changes induced in rabbits by unfractioned horse serum. The suppression of glomerular proliferation by cortisone was associated with focal glomerular necrosis suggestive of the Kimmelstiel-Wilson lesion; this did not occur in the animals treated with ACTH. (3) Hawn and his group [*11*] noted chiefly beneficial histologic effects on renal lesions induced by heterologous plasma protein fractions. (4) Thomas and co-workers [*12*] noted marked accentuation of the renal cortical necrosis associated with the generalized Shwartzman phenomenon.

* Thus one of us (S. H. A., Jr.) was given, ten years ago, the opportunity to examine a painstaking study of the effect (or lack of it) of these agents on serial Addis counts in a group of unpublished adult men with smouldering "latent nephritis" [*13*].

literature.* While reports in the adult literature are too sparse to yield any valid appraisal of incidence in our colleagues' adult service, three closely spaced encounters with the cruciate course in 1955 brought an end to our systematic use of these drugs in adults with nephrosis at Cook County Hospital.

At the time this seemed consistent with a mounting consensus stated in Allen's 1955 clinical and pathologic recapitulation of the nephrotic syndrome [*20*]: "The dictum ACTH and cortisone cure nothing applies also, . . . the evidence is far from clear-cut that they appreciably prolong life from the viewpoint of group survival."

THE PROBLEM OF PROGNOSTIC APPRAISAL OF THE UNTREATED SUBJECT WITH NEPHROSIS

Nevertheless, at this time there began to be heard among the pediatricians some more hopeful voices, and among these could be counted an occasional internist [*21*]. A clinical impression developed that patients maintained on various schedules of continuous adrenocorticoid therapy (in contrast to patients whose therapy ended with diuresis or failure thereof) lived longer than untreated patients. Prominent among the proponents of this view was the group of Lange in New York who, indeed, in the very early 1950's had predicated their regimen of treatment directly on the concept of a hyperimmune pathogenesis of the glomerulonephritic nephrotic syndrome* [*22*] based on their observation of lowered serum complement which ACTH restored. While these observations diverge from others' experimental studies [*26*], the resultant orientation of their clinical investigative program enabled them to present a provocative series of five-year survivals for a small group (including both children and adults) at a time when few others had more than two years of continuous therapy to appraise.

There followed a valiant attempt to validate these clinical impressions in a statistical fashion; an attempt that brought collaboration of many pediatricians. Thus Riley [*27*], in reviewing his own material in the ACTH-cortisone period, noted no change in ratio of deaths to "cures," but did have evidence for an increased survival time as well as decreased symptomatic disability. He set out to corroborate this by the application of a modified life table method to data on 780 children with nephrosis selected from 1,300 candidates submitted by eighteen investigators in fourteen cities.

Statistical problems were clearly recognized by the collaborating clinicians. In the Seventh Annual Conferences on the Nephrotic Syndrome (p. 213, 1955 [*1*]), in response to a statistician's comment: "you have to alternate not treating patients or you are not going to get a definite answer," there emerged two inherent difficulties of the alternate case method: (1) *The parental grapevine difficulty:* namely that parents of children with nephrosis tend to intercommunicate, and even with a double-blind technic can easily tell whether or not their child is getting the supposedly magic steroids. If not, they tend to change medical advice. (2) *The age-old problem of the physician's sense of humanity as opposed to his*

* The spontaneous development of sudden hypertension which (if a prior nephritic history is not known) can be mistaken for a fulminating malignant hypertension is rare enough to be a subject for individual case presentations in the literature [*15,16*]. In our experience, the development of this rarity is measured in months rather than weeks.

In an early report from the Children's Medical Center, Boston, a transient and reversible azotemic episode was observed in six of forty-five treated patients, and one of their four deaths was related to precipitation of hypertension [*17*]. A subsequent report noted azotemia in eleven of the eighteen fatalities among 153 children with nephrosis who received short-term therapy with ACTH or cortisone.

More recently, Berman [*18*] describes a five year old boy who "became anuric while receiving steroids and remained so for sixty days supported by hemodialysis" until death.

Riley (Proceedings of the Seventh Annual Conference, p. 198, 1956 [*1*]) expresses concern about the problem of adequate statistics on spontaneous changes over time in children's nephrotic syndrome: "The thing that worries me more than cases that are so mild . . . they would not be recognized . . . is the case . . . that will not tolerate hormone treatment; . . . you . . . start him . . . run three or four days and then discover the blood pressure shooting way up and the NPN shooting way up, so you stop. You may try again, and the same thing happens, so you stop . . . "

Grossman [*19*] recently has shown us a child in whom simultaneous exhibition of steroid and rauwolfia alkaloid was not accompanied by the precipitous hypertension which on previous trial of steroids alone had forced their withdrawal.

* While the hyperimmune hypothesis of pathogenesis (first based on correspondence of latency of the acute hemorrhagic disease with latency of serum sickness) was already venerable [*23,24*], and while considerable supporting experimental and clinical evidence had appeared, precise details of mechanism in glomerulonephritis (particularly in the chronic form presenting as the nephrotic syndrome) was then certainly no clearer than today. An excellent review of these problems has recently appeared [*25*].

statistical critique: a growing clinical conviction of longer survival, as well as less compromised day-to-day living made it hard for pediatricians to withhold therapy from a child on the basis of the child's order of appearance.

However, given absence of alternate cases,* the encouragement obtained by pooling the series which individually had yielded favorable clinical impressions kept therapy going in pediatric centers. The appearance of the delta$_1$ unsaturated steroids (prednisone and prednisolone, and later triamcinalone), which further minimized mineralocorticoid effects, provided an added stimulus.

Our own decision to resume trial of steroids (now on a large dosage, continuous basis) in adults with nephrotic glomerulonephritis came by reason of personal communications from Kark and his group on the course of certain of their patients with lupus nephropathy. Published last fall in preliminary fashion [*32*], this study indicates prolongation of average survival by at least a year as compared to a clinically matched group treated with small doses of cortisone. All of the latter were dead within a year.

It is true that evidence for continued operation of abnormal hyperimmune mechanisms in disseminated lupus is more substantial than in the later phases of chronic glomerulonephritis† [*33*], and non-renal manifestations are well known to be symptomatically amenable to the anti-inflammatory effects of certain adrenal steroids. It is true that the control group was not constructed on alternate cases. But this study is a milestone in the favorable prognostic influence of adrenocorticosteroid therapy.

THE PROBLEM OF PROGNOSIS IN THE ADULT

Addis warned against figures representing prognosis in the nephrotic syndrome [*14*]: "Polemics about the proportions of patients that heal or die of uremia are vain because our figures . . . will be determined . . . by . . . the sort of patients that are referred to us and many other local and individual factors . . . most of these circumstances tend toward too gloomy a view."* But without some quantitation of prognosis in the untreated state (which, as a starting point, may be as crude as the number and life spans of patients who die in uremia), no therapeutic regimen can be evaluated. Addis did give some figures on life span of his patients with nephrosis who died in uremia. Figure 2 schematically illustrates these together with comparable results obtained by Ellis in London (about a decade earlier), and the figures our renal team obtained prior to intensive continuous high dosage steroid therapy. The results in London and San Francisco show a remarkable similarity.

Whatever be the "local and individual factors" differentiating London, Chicago and San Francisco,† the pressure felt by our renal team for

* The argument for alternation of cases in a controlled study (in elimination of spontaneous year-to-year fluctuations in disease severity) has real validity in the instance of acute hemorrhagic glomerulonephritis.

To our knowledge, a patient so diagnosed has not died in the acute stage in our adult medical service in some five years, nor have we seen a total anuria. In a single year at the turn of the half century one of us cared for two ultimate fatalities in anuria (one of these despite four hemodialyses), and observed several others with nearly complete anuria.

Markowitz [*28*] in reporting a correlation (as a function of animal passage)—between virulence and experimental nephritogenic capacity of Type 12 streptococci recovered from acute nephritics, may provide a basis for these year-to-year variations.

Again, with reference to progression toward chronicity, Earle [*29*] has pointed out differences between adults who present in a civilian urban medical center, and young military personnel who contract the streptococcal [*30*] or non-streptococcal related syndrome [*31*] in training camps.

† In the history of immunological thinking in this syndrome, it is worth recalling the speculation now thirty years old [*34,35*] that an *absence* of normal immune responsiveness to products of beta hemolytic streptococci characterizes those patients who progress from a known or hypothetical acute hemorrhagic glomerulonephritis to chronicity. Today, to be reconciled with reports of the application of Coons' technic to renal biopsy and autopsy material [*36*], and the fact that a kidney transplanted from a healthy donor into an identical twin with glomerulonephritis has developed histologic evidence of nephritis [*25*], stands a curious fact, that nephrotic glomerulonephritis progressing to uremia has been described in a premature infant; the progression took place during a period when maternal antibodies should be disappearing and the infant's own ability to synthesize gamma globulins should be minimal [*37*]. Perhaps reconciliation lies in the length of time antibody remains bound to renal structure (*vide*, Proceedings of the Ninth Annual Conference on the Nephrotic Syndrome, p. 161).

* Doubtless, this comment was prompted by a difference in incidence of chronic manifestations following an acute hemorrhagic nephritic episode between patients in San Francisco under his own scrutiny, and patients in Rochester (N. Y.) observed by one of his own students [*38*].

† Presumably Ellis' and Addis' patients numbered few Negroes (this is not stated in their publications), and

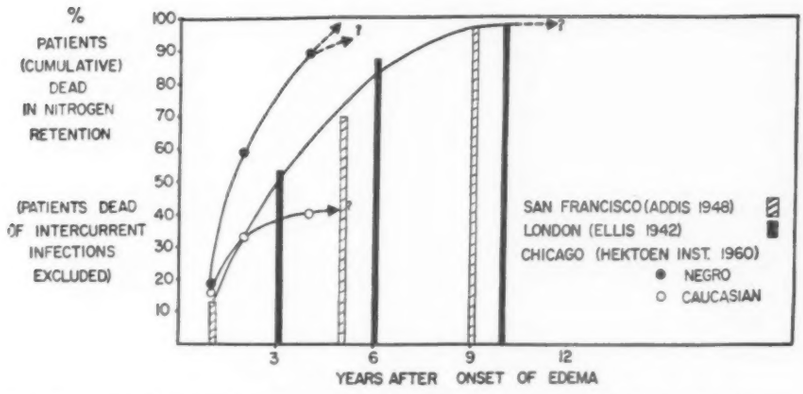


FIG. 2. These plots on duration of life between the discovery of the nephrotic syndrome and death in nitrogen retention for San Francisco are taken from reference 14, p. 219; for London, from reference 53; for Chicago, from the unpublished data the authors and their co-workers have collected over the last five years.

grasping at any straw pointing toward increasing longevity is evident by the Chicago life span plot for the postpuberal Negro with chronic membranous glomerulonephritis who presents with the nephrotic syndrome. While our Chicago Caucasian life span plot is in accord with Luetscher's notation "death in uremia of 40 per cent of patients with chronic membranous glomerulonephritis in five years" [*39*], 40 per cent of our Negro patients have died in nitrogen retention within *one* year, nearly *90 per cent* within four years.*

Our next concern (rather than a review of all the straws in the literature of the late 1950's which pointed toward intensive continuous high steroid therapy*) is to consider the clinical problems we have met in our own efforts to document the relationship between treatment and any significant prolongation of life, for it is essential to justify the discomforts, inconveniences and dangers we are imposing in iatrogenic Cushing's syndrome.

CUSHING'S SYNDROME: SPONTANEOUS AND IATROGENIC IN RHEUMATOID ARTHRITIS AND IN BRIGHT'S DISEASE

In the beginning of the adrenal corticoid era, a noted rheumatologist compared treating a pa-

contained some children (ours are adults only). Ellis' patients were studied in the pre-antibiotic era, and both series were studied in the pre-steroid era.

Other differences may well be expected between the population of those with nephrosis who present themselves (usually by referral of private physicians) to the nephritic clinic of a shipshape Bristol fashion medical school hospital (with a chief widely known for personal convictions on mechanisms and management of Bright's disease), and the population of those with nephrosis who reach the attention of the consulting renal team in a vast municipal hospital whose ward patients are chosen chiefly by interns from some 1,000 who pass daily through the admitting floor, and where outpatient study is limited to longitudinal follow-up.

* The latter resembles those given by Barnett and Eder for patients over thirty years of age in the Rockefeller Hospital series [*40*], and Post's small Cleveland adult series of whom 70 per cent were dead in three years (The Tenth Annual Conference on the Nephrotic Syndrome, p. 236 [*1*]).

Luetscher's as well as Addis' clinical spectrum included children, and their figures are in agreement with Rennie in Glasgow [*41*] whose series had an age range between four and sixty. If only postpuberal patients in Rennie's study are included, the resultant life span plot lies closer to that for our Negro patients than to that of Ellis'-Addis' data (Fig. 2).

* The discussion of steroid therapy in the Tenth Annual Conference on the Nephrotic Syndrome contains a representative array, many of which are sufficiently substantial to belie the word straw. Thus we could not fail to be impressed by Post's description of two adult Negro women in his small group reported alive and well on maintenance steroids three years after the onset of the nephrotic syndrome. In our larger untreated group, we have no such patients alive.

Again Lange's fifteen of sixteen adults alive and free of both edema and azotemia surpass any expectations based on Figure 2 [*42*].

It is true that, in common with many workers, we have in follow-up untreated Caucasian adult patients who have lived normal lives for an unusually long time following full-blown biopsy substantiated glomerulonephritic nephrosis. In reports dealing with unusually long survivals [*43–45*] Negroes are notable in scarcity, perhaps because race is not uniformly stated. They do exist, however; thus Pollak has studied [*46*] an adult Negro woman much resembling a patient reported by Rytand [*43*].



FIG. 3. *Left*, before therapy. *Right*, after therapy.

tient with rheumatoid arthritis with grabbing a large bear by the tail. Today, if used at all, "the goal . . . is to induce *suboptimal* (italics ours) relief of symptoms in a prolonged severe exacerbation," [*47*] and in conjunction with physical, climatological and even psychotherapeutic measures. The full-blown iatrogenic Cushing's syndrome familiar in arthritic clinics ten years ago has melted into a milder form. Even so, experienced rheumatologists are still far from happy. In 1955 Howell and Ragan reported termination of adrenocorticoid therapy in twenty-seven of sixty-eight patients "because of untoward events." At this writing, the recent literature contains some very unhappy pictures, verbal and photographic, of iatrogenic Cushing's syndrome in rheumatoid arthritis [*48*,*49*].

When the problem is pain, limitation of motion, or deformity, one can justifiably say to the patient: "These don't kill. We will rely upon steroids just as little as your tolerance for discomfort and ability to function will let us." By contrast, in Bright's disease the inexorable fibrosis leading to glomerular hyalinization, tubular dilatation atrophy, and ultimate destruction of individual nephrons is a painless process, and can even be associated for long periods with subjective well-being such that the patient does not even have relief of pain or gain in mobility as compensation for the outward appearance and inner symptoms therapy brings. Even the initial compensation of a diuresis (when it occurs) is soon negated by the salt and water retention occasioned by continuous use of steroids of reputedly minimal mineralocorticoid potency.

Spontaneous Cushing's syndrome, irrespective of histopathologic basis, is usually considered universally fatal in a few years unless successfully treated. Despite the use of many available modalities of treatment, a mortality as great as 50 per cent within five years has been reported [*50*]; a figure similar to Luetscher's (*vide supra*) for untreated patients with nephrotic Bright's disease.

While nearly all the unsightly, uncomfortable or dangerous manifestations of spontaneous Cushing's have been described in connection with the iatrogenic syndrome, its mortality has not been of this order of magnitude, for the physician can select the steroid and vary the overdose. Today's iatrogenic mortality applies to therapy of many syndromes which have in common with rheumatoid arthritis the aim "suboptimal relief." What does *suboptimal relief* mean when referred to progressive nephron replacement by fibrous tissue? Many students of continuous therapy in adults with nephritis have tried to attenuate the manifestations of Cushing's syndrome by small dosages* and by steroid-free parts of each week, and still maintain the continuity of whatever anti-scarring effect the steroids may have. Some success has attended these efforts. But, in terms of sex, race, histologic classification of lesion [*51*] and parameters of renal function, the lower limits to which one may go in attenuation of the Cushing's syndrome and still retain *any* anti-scarring potency are not defined. When faced with a mortality such as we have in our adults (Fig. 2) one is tempted to ask the patient to withstand a more continuous and florid Cushing's syndrome than has been hitherto imposed in many therapeutic regimens (Fig. 3).

Reversing the "before and after" pictures sometimes shown by delighted surgeons, the situation depicted in Figure 3 (right) is tolerated by an unusually intelligent person (with an understanding family) under well nigh weekly meticulous observation; outpatient when things are going well, inpatient when not. Perhaps, in part, the patient's tolerance comes through the physician's reassurance that indices of renal function and histology reflect a happier picture in the kidney than in the face on the right.

As a further example, we list the following sequences for another patient we have treated continuously for over eighteen months (first with massive doses, always with a dose approximating 40 mg. of prednisolone a day) with apparent stabilization of renal function in a fashion his prior course did not portend.

* The effect of a given dosage shows great individual variation. In some persons a florid Cushing's syndrome can be sustained on but 10 to 15 mg. prednisolone ingested daily.

PROBLEM	MANAGEMENT
Fourth day: systolic and diastolic hypertension; retinal arteriolar narrowing; increase in peripheral edema and ascites.	Diuril, moderate success.
Second week: psychosis* (attempted to jump out of sixth story hospital window).	Restraints; tranquilizers; steroid therapy stopped for five days.
End of first month: persistent psychosis; paranoid ideas; socially unacceptable behavior on the ward.	Steroids continued at a level of 125 mg./day (with misgivings).
Sixth week: spontaneous regression of psychosis; alternating diarrhea and constipation; Shigella cultured from stool.	Sulfadiazine.
Seventh week: rising urine output (>4 L./day); gastric cramps; hyponatremia (sodium 115, chloride 87, potassium 3.9 mEq./L. serum).	Steroids reduced to 36 mg./day.
Eighth week: "psychogenic" diabetes insipidus; pitressin-sensitive urine output, 13–20 liters/day; positive Hickey-Hare test.	None.
Thirteenth week: pyelonephritis, Aerobacter aerogenes; sensitive only to polymixin and kanamycin.	Cautious intramuscular kanamycin.
Fifteenth week: diarrhea and abdominal pain; Endamoeba histolytica recovered from the stools.	Chloroquin; diiodoquin.

We will not carry this narrative here from the fifteenth week to the eighteenth month. Suffice it to say that if this patient had been gainfully employed, a very high price in lost wages and an enormous hospital bill would have to be payed for the apparent present stabilization of the renal lesion, a price that needs meticulous and individual consideration whenever this level of iatrogenic Cushing's syndrome is contemplated. While he is indeed at one end of the range, no patient has in our hands escaped at least one complication of therapy. We have encountered some quite rare in the iatrogenic literature (e.g., the precipitation of a full-blown diabetic acidosis in a previously non-diabetic young girl who had older relatives with diabetes).

At present, we can comment upon our experience with dosage levels as follows: (1) Heroic doses: (e.g., 500 mg. of prednisolone or more a day) are likely to be forced to a reduction in a matter of days.† (2) Doses in the range of 100 mg./day of prednisolone are very likely to be forced to reduction in a matter of weeks. (3) Maintenance doses in the range of 40 mg. prednisolone produce an iatrogenic Cushing's syndrome the complications of which (despite every ancillary precaution) require the most constant observation.

Since using delta$_1$ unsaturated steroids, we have not seen any cruciate courses. No one has progressed into uremia faster than anticipated for the untreated state. *However*, no patient has been saved from uremic death who, prior to treatment, gave evidence of nitrogen retention on the verge of becoming symptomatic.

Our own data do not let us say as yet whether lengthened life spans will prove as encouraging in biopsy-established chronic membranous glomerulonephritis as they have in lupus nephropathies, some of which were treated under working conditions not too different from ours. But other workers are encouraged [*51*]. If this encouragement spreads, then (irrespective of convictions on streptococcal relatedness or unrelatedness of chronic phases of Bright's disease) one must ask: should the nephrotic syndrome remain the basis of selection for treatment?

In analogy with experimentally produced glomerulonephritis, the disease in man is known to proceed at variable rates to a uremic death without ever developing the nephrotic syndrome. So, also, do a small but definite proportion of pa-

* There was no prior history of psychopathy beyond a sporadic fondness for ethanol. Our experience is in agreement with Danowski's studies in adolescents and adults: among complications, "anxiety, confusion or psychosis is a leading manifestation" [*51*]. In common with reports of iatrogenic Cushing's in hematologic disorders [*52*] we have encountered muscular weakness unrelated to serum electrolyte abnormalities.

† Here, our experience is quite similar to that of Dr. S. O. Schwartz and colleagues (personal communication) in trials of heroic doses in certain forms of Hodgkin's disease and leukemia.

tients with acute hemorrhagic streptococcal related glomerulonephritis. Because the rates of progression of these forms of glomerulonephritis are so variable, because existing reports on histological types other than the chronic membranous range from lukewarm to discouraging [*51*], because the drawbacks of iatrogenic Cushing's syndrome are so great, we are not yet ready to subject such patients to adrenocorticoid therapy.

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Clinical Studies

Hypoalbuminemia (with Anasarca) Due to Hypercatabolism, Serum Protein Exudation into the Gastrointestinal Tract, Increased Capillary Permeability and Hypoanabolism*

The Unusual Occurrence of Increased Capillary Permeability Temporarily Reversed by Human Growth Hormone Therapy

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HYPOALBUMINEMIA severe enough to cause edema may be due to an inadequate dietary intake of protein, an intestinal malabsorption syndrome, impaired hepatic function resulting in diminished synthesis, the external loss of plasma proteins, hypercatabolism or increased peripheral capillary permeability. Often several of these etiologic factors coexist. For example, the chronic alcoholic may have not only a poor dietary intake of protein but also cirrhosis of the liver, both of which result in a diminished hepatic capacity to synthesize plasma albumin [*1*]. The patient with the nephrotic syndrome may both lose large amounts of albumin externally through the kidneys as a result of increased glomerular capillary permeability, and simultaneously catabolize albumin at an increased fractional rate [*2*]. The patient described in this report presented clinically with generalized edema and hypoproteinemia predominantly affecting the albumin fraction. The mechanism of the hypoalbuminemia, as investigated by a turnover study with albumin labeled with radioactive iodine (I^{131}), suggested that several pathophysiological mechanisms were responsible, including an increase in the fractional rate of catabolism, an increase in peripheral capillary permeability, a loss of plasma albumin into the gastrointestinal tract, and a decrease in the rate of serum albumin synthesis.

CASE REPORT

This fifty-nine year old white, male carpenter (E. T.) was referred to the Peter Bent Brigham Hospital in December 1957. He had a two and a half year history of hypoproteinemia and hypoalbuminemia of unknown etiology and a two-year history of generalized edema. For approximately twenty years he had drunk three to six bottles of beer a day, but his dietary intake during that time was adequate. He had a fifteen-year history of mild abdominal distress with bloating, epigastric pain, and occasional vomiting and diarrhea. In June 1955, cholecystectomy was performed following an episode of intense pain in the right upper quadrant, with vomiting. Microscopic examination showed chronic inflammation of the gallbladder, but no stones were found in the gallbladder or the ducts. At laparotomy the pylorus was thought

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to be thickened. No ascitic fluid was present and the remaining abdominal organs were not abnormal.

Hypoproteinemia was noted as early as March 1955 when the total protein was found to be 4.7 and the serum albumin 2.6 gm. per cent. In the fall of 1955 there was an insidious onset of generalized edema. The patient was treated with digitalis and diuretics without remission of the edema or hypoproteinemia. In May 1956 persistent hypoproteinemia (total protein of 4.5 and albumin of 2.5 gm. per cent) and hypercholesterolemia (345 mg. per cent, 71 per cent esters) were noted. In July 1957 the serum albumin fell to its lowest point of 0.8 gm. per cent (total protein 2.3 gm. per cent) while cholesterol rose to its highest point of 500 mg. per cent (50 per cent esters) and the serum became lactescent. The patient was given a high protein, high carbohydrate, low fat and low cholesterol diet, vitamins, and intravenous albumin and blood infusions. The administration of digitalis and diuretics was discontinued. His response was satisfactory as reflected by an increase in total protein to 4.7 gm. per cent and in albumin to 2.6 gm. per cent with the disappearance of edema, a decrease in the cholesterol to 295 mg. per cent (69 per cent esters), and a disappearance of serum lactescence.

The amelioration was of short duration, however, and three months later (October 1957) edema recurred, the serum albumin fell to 1 gm. per cent, and the serum cholesterol rose to 400 mg. per cent. The previous high protein dietary regimen was reinstituted without improvement of the edema or serum protein.

There was no family history of protein or lipid disorders. The patient's daughter had a normal serum protein and cholesterol level.

On admission (December 11, 1957) the patient was a chronically ill, edematous, white man in acute distress. (Fig. 1.) He weighed 81 kg. (His normal edema-free weight was 65 kg.) There was no retinopathy. The neck veins were not distended and there was no periorbital edema. Chest expansion and aeration were poor, particularly at the bases where there were signs of pleural effusion. The heart was normal. The abdomen was distended and there was shifting dullness. There was no fluid wave. The liver was not enlarged. The spleen and kidneys were not palpable. There was 4-plus pitting edema of the feet, ankles and legs, 2-plus pitting edema of the thighs without phlebitis, and 3-plus pitting edema over the sacrum. The genitalia and abdominal wall had 1-plus pitting edema extending up to the lower thorax. Peripheral pulses were present and equal bilaterally. There were no xanthomatous lesions of the skin or tendons. The spine was not tender or deformed. Examination of the rectum and prostate gland was within normal limits. Neurological examination revealed no abnormalities except for diminished auditory acuity.

The hemogram, urinalysis, renal function tests and serum electrolytes were generally within normal limits. The hematocrit was 38 per cent, with normal red cell morphology and platelet count. The leukocyte count was 6,800/cu. mm. with a normal differential. The corrected erythrocyte sedimentation rate (Wintrobe) was increased, averaging 38 mm. per hour. Urinalysis showed no proteinuria, glycosuria or pyuria. The urine specific gravity varied from 1.010 to 1.026. The blood urea nitrogen was 11 mg. per cent, non-protein nitrogen 30 mg. per cent, and uric acid 3.1 mg. per cent. Phenolsulfonphthalein excretion was 20 per cent in fifteen minutes and 70 per cent in



FIG. 1. Patient (E. T., PBBH No. 5L839) with anasarca. Note the striking edema of the lower extremities, ascites with everted umbilicus and marked wasting of musculature.

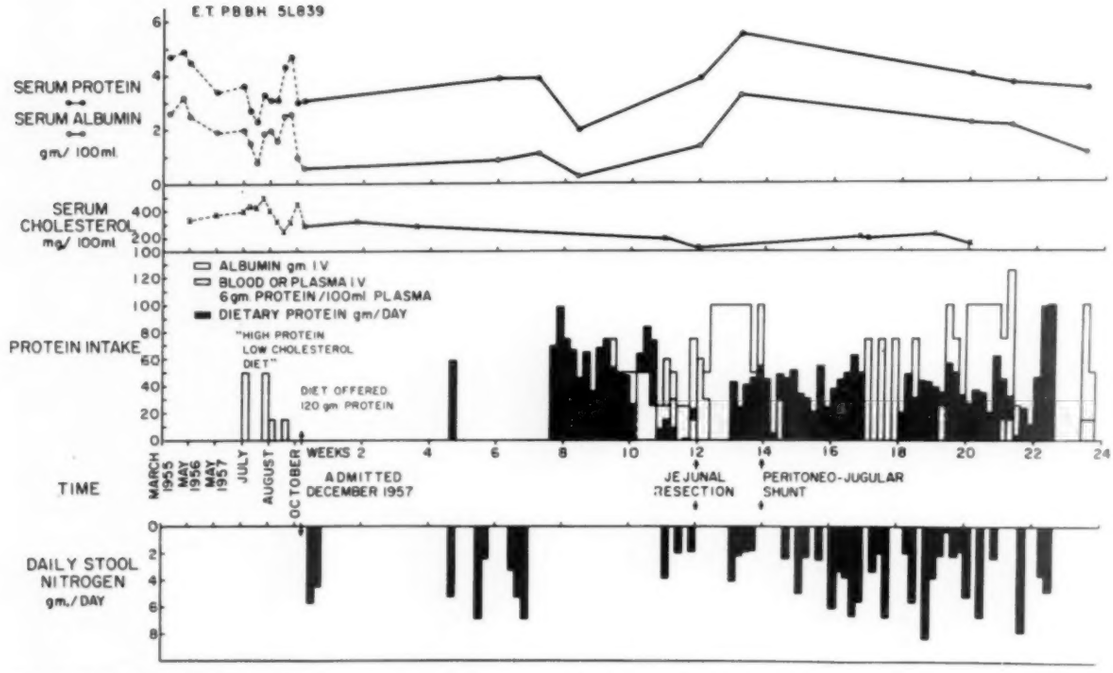


FIG. 2. Protein and nitrogen balance over a three-year period, including twenty-four weeks of hospitalization at the Peter Bent Brigham Hospital. Dotted line represents protein, albumin and cholesterol data obtained over a two-and-a-half-year period prior to admission. The following points are noteworthy: (1) Hypoalbuminemia and hypoproteinemia were documented two and a half years prior to admission. (2) Cholesterol level varied inversely with the albumin level. Maximum serum cholesterol concentrations occurred with lowest albumin concentrations. Cholesterol fell to lowest levels with intensive intravenous albumin infusions. (3) Despite intravenous albumin infusions of 100 gm. per day for a period of ten days, the patient's serum albumin concentration failed to rise to normal. (4) Daily fecal excretion of nitrogen exceeded twice the normal value of less than 2 gm. per day, even while on a normal dietary protein intake of 70 gm. per day and without apparent evidence of impaired protein digestion.

two hours. The serum sodium ranged from 122 to 141 mEq./L., potassium 2.7 to 5.6 mEq./L., bicarbonate 15.3 to 29.9 mEq./L., and chloride 90 to 109 mEq./L. The serum cholesterol was 295 mg. per cent on admission. A Congo Red test was normal (44 per cent uptake by the tissues). The reaction to a blood serologic test for syphilis was negative.

Liver function studies revealed no evidence of parenchymal damage but there were abnormal flocculation reactions consistent with the alteration in the serum proteins. The serum bilirubin was 0.19 mg. per cent, the alkaline phosphatase 1.6 Bodansky units. Bromsulphalein retention was 2 per cent in forty-five minutes. Prothrombin activity was 100 per cent of control. The serum lactic acid dehydrogenase, transaminase and cholinesterase were normal. Thymol and cephalin flocculation tests were each 4 plus (normal 0 to 1 plus).

Protein and nitrogen balance studies over a three-year period are summarized in Figure 2. The serum total protein on admission was 3.1 gm. per cent by Kjeldahl analysis. Paper electrophoretic fractionation revealed: albumin 0.6 gm. per cent, alpha$_1$-globulin 0.29 gm. per cent, alpha$_2$-globulin 0.97 gm. per cent, beta globulin 0.55 gm. per cent, and gamma globulin 0.68 gm. per cent. (Table I.) A free electrophoresis,* performed because of the striking alpha$_2$-globulin peak, did not demonstrate the special component of the alpha$_2$-globulin often seen in patients with primary familial amyloid disease [*3*]. Starch gel electrophoresis† demonstrated a sharp, intensely staining band of gamma globulin migrating with the most basic fraction of slowest mobility, similar to that seen in multiple myeloma. Ultracentrifugal analysis† showed this gamma globulin peak to have a sedimentation constant of 7 S (Svedberg units), indicating a molecular weight of about 160,000, similar to that of normal gamma globulin. The beta iron-binding globulin, determined immunologically [*4*], was 105 mg. per cent, markedly below the normal range of 210 to 310 mg. per cent. Ceruloplasmin, determined by a spectrophotometric method measuring copper oxidase activity [*5*], was 11 mg. per cent, markedly below the normal range of 20 to 30 mg. per cent. Paper electrophoresis of fresh serum revealed a slight increase in

* Kindly performed by Dr. Evan Calkins, Massachusetts General Hospital, Boston.

† Kindly performed by Dr. Henry G. Kunkel, Hospital of the Rockefeller Institute for Medical Research, New York.

TABLE 1
REPRESENTATIVE PROTEIN CONCENTRATIONS PRIOR TO ALBUMIN THERAPY

Data	Values in Patient E. T. (gm./100 ml.)	Normal Values (gm./100 ml.)
Serum		
Total protein	3.84*	6.0 to 8.0
Albumin§	0.58 0.57†	3.5 to 4.5
Alpha$_1$-globulin§	0.23	0.3 to 0.5
Alpha$_2$-globulin§	1.00	0.5 to 0.7
Beta§	0.81	0.8 to 1.0
Gamma§	1.23	0.8 to 1.2
Ceruloplasmin	0.011‡	0.020 to 0.030
Beta iron binding globulin	0.105†	0.210 to 0.310
Edema		
Total protein	0.240*	...
Albumin	0.175†	...

NOTE: For normal values in edema see "Comments."
* Kjeldahl determination.
† Immunologic determination [4]
‡ Copper oxidase method [5]
§ Paper electrophoresis.

lipoproteins migrating both with the beta globulins and with a mobility intermediate between the beta and alpha$_2$-globulins.

Two studies of albumin metabolism using radioiodinated human serum albumin (RISA) showed a reduced half-life of 4.9 and 5.7 days, compared with values of 10.5 and 11 days in two control subjects. Amino acid determinations* of plasma, urine, erythrocytes and leukocytes were within normal limits [6]. Edema fluid total protein was 240 mg. per cent by Kjeldahl analysis and albumin 175 mg. per cent by immunological determination [4]. Electrophoretic analysis of ascitic fluid showed a low alpha$_2$-globulin concentration, in marked contrast to the elevated serum alpha$_2$-globulin concentration.

The total nitrogen in the stool was consistently increased [7]. The daily stool nitrogen ranged from 2 to 8 gm., the normal value being less than 2 gm. per day [8]. The daily urinary excretion of nitrogen was within normal limits (10.1 to 14.8 gm.), the normal range being 11 to 15 gm. per day, while on a normal protein intake of 70 to 80 gm. per day [8]. The total urinary nitrogen was partitioned into amino acid, creatinine, urea and uric acid nitrogen, and each was within normal limits.

* Kindly performed by Dr. R. H. McMenamy, Department of Physical Chemistry, Harvard Medical School, Boston.

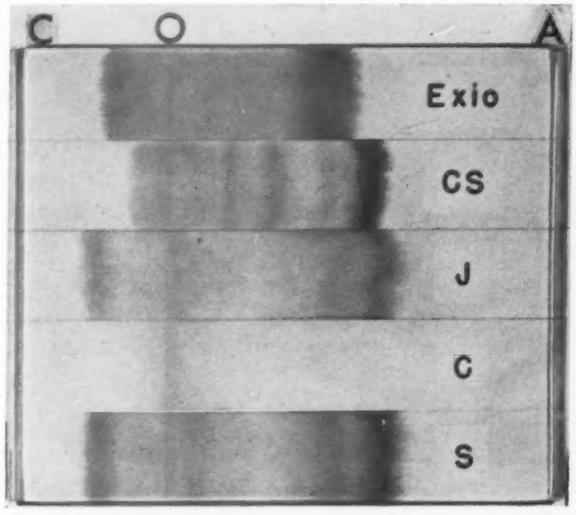


FIG. 3. Paper electrophoresis. "O" symbolizes the point of origin where samples were applied. "C" represents cathode (negative pole) and "A" anode (positive pole). E × 10 = Edema fluid of patient (E. T.), concentrated ten times, shows albumin at anodal side and gamma globulin at cathodal side. Gamma globulin has moved toward the cathodal side of the point of origin due to electroendosmotic flow. CS = Control serum after electrophoresis shows all the serum protein fractions. J = Jejunal juice of patient (E. T.) after concentration and electrophoresis shows albumin, alpha$_1$- and gamma globulin. C = Jejunal juice of a normal control subject, after concentration and electrophoresis in a manner identical to that applied to the jejunal juice of patient (E. T.), failed to show any protein. S = Stomach juice of patient (E. T.), after concentration and electrophoresis, shows albumin, alpha$_1$- and gamma globulin.

The striking loss of nitrogen in the stool suggested the possibility that serum proteins were leaking into the gastrointestinal tract and led to further studies on the intestinal fluids. Gastric and jejunal juices were obtained for paper electrophoresis from the patient and from a normal control subject in the fasting state. They were lyophilized and concentrated to achieve an adequate protein concentration. Edema fluid was also obtained from the patient and concentrated ten times. The electrophoretic patterns are shown in Figure 3. Three proteins were found in the patient's stomach and jejunal juice and edema fluid. These proteins moved with the mobilities of albumin, alpha$_1$- and gamma globulin. No alpha$_2$- or beta globulins were noted. By contrast, the jejunal fluid of the control subject lacked the three proteins and showed only a trace of material at the point of origin.

Immunoelectrophoresis [9] was performed to show that these proteins in the intestinal juice were serum proteins and not mucoproteins of a similar electrophoretic mobility. Electrophoresis of gastric juice was performed in agar, as shown in Figure 4 (lower strip marked 0–2). In a trough cut parallel to the axis of migration, labeled "C," horse antiserum against all

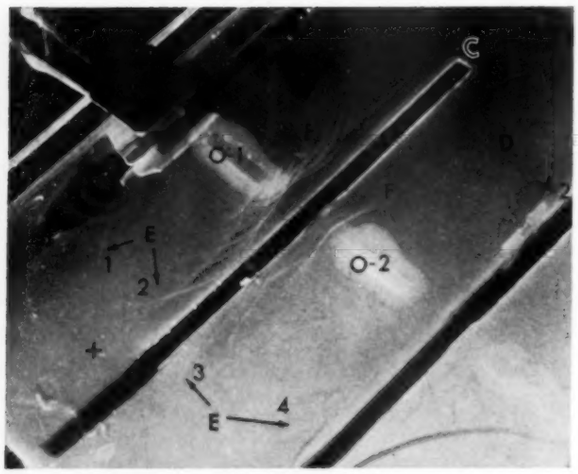


FIG. 4. Immunoelectrophoresis in agar gel. 0–1 represents point of origin of control serum migrating toward anode. In the trough labeled C, parallel to the axis of migration, was placed horse antiserum prepared against the many antigens found in normal human serum. Opaque arcs are noted where antigen and antibody precipitated in the zone of equivalence. For example, the arc labeled E 2 represents albumin. In the trough labeled A_1 horse antiserum prepared against human albumin was placed. An opaque arc of precipitation is noted and labeled E 1. At point of origin, 0–2, gastric juice from patient (E. T.) was placed and electrophoresis performed. These electrophoretic protein fractions found in the gastric juice were reacted with the same horse antisera as used in the control studies above (trough A_2 and C). Four lines of precipitation were found where the antiserum in trough C reacted with proteins from the gastric juice. In trough A_2 where antiserum against serum albumin *alone* was placed a single arc of precipitation was found, labeled E 4. These studies indicate that there were four proteins immunologically identical to normal serum proteins in the gastric juice of patient (E. T.). One of these proteins was identical to serum albumin. The other three were presumably serum globulins.

normal human serum proteins was placed. The theory of this technic is that both antibody and antigen will diffuse toward each other through the agar gel. When both meet in a zone of equivalence, there is precipitation recognizable as a thin white arc. Four arcs were visible where the antiserum in "C" reacted with the electrophoretic fractions, indicating the presence of four serum proteins in the gastric juice. Since one of these arcs (labeled E 3) was found to be identical with the arc (labeled E 4) formed between these proteins and specific antiserum to serum albumin, it can be assumed that the gastric juice contained serum albumin and three serum globulins. In the upper strip (labeled 0–1) a control immunoelectrophoresis of normal serum was performed. The many arcs representing different immunological serum proteins can be identified. Again the identity of the albumin arcs was seen to be the same for both antiserums (labeled E 1 and E 2).

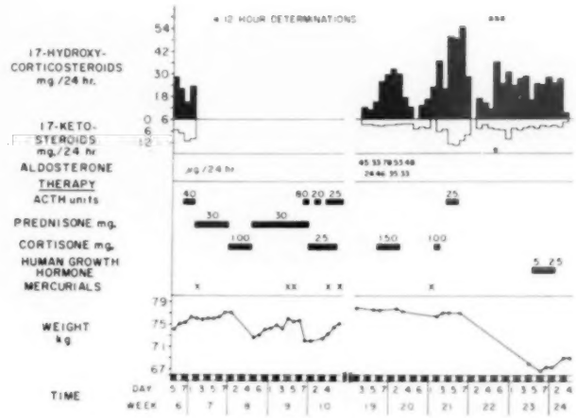


FIG. 5. Steroid excretion and therapy. The following points are noteworthy: (1) The high baseline excretion of 17-hydroxycorticosteroids (16 and 21 mg. per twenty-four hours compared to normal values of 1 to 10 mg. per twenty-four hours), and the brisk response of both 17-hydroxycorticosteroids and 17-ketosteroids to stimulation with intravenously administered ACTH, during the twenty-first week, are consistent with adrenal hyperfunction. ACTH was given intramuscularly on all occasions except during the twenty-first week. Adrenal function can be adequately assayed only after ACTH has been given intravenously. (2) The elevated urinary aldosterone values (24 to 78 μg. per twenty-four hours compared to normal values of 1 to 10 μg.) were obtained while the patient was on severe dietary sodium restriction (5 to 10 mEq. daily) and are consistent with values obtained in patients with secondary hyperaldosteronism. (3) The marked weight loss between the twenty-first and twenty-third weeks was concurrent with the infusion of massive amounts of albumin, resulting in diuresis, and progressive clinical deterioration with continued gastrointestinal protein wasting.

Tests of protein digestion and absorption failed to indicate any abnormalities which might clearly explain the high content of nitrogen in the stool. An oral casein (proline) absorption test was within normal limits.* Trypsin and chymotrypsin enzyme activity in the duodenal juice was present, but somewhat reduced below normal.* No undigested meat fibers were noted in the stools. Dr. T. H. Wilson of Harvard Medical School demonstrated that a portion of surgically resected jejunum was unable to transport radioactive albumin from the serosal to mucosal surface, which was considered to be one possible mechanism of serum protein exudation into the intestinal tract. The jejunal specimen was viable since it was able to transfer glucose from the mucosal to the serosal surface against a concentration gradient [*10*].

Tests of fat and carbohydrate digestion showed no striking abnormalities. The result of a butterfat absorption test was normal. Serum carotene, serum vitamin A, serum lipase and duodenal lipase activity were normal. Stool fat was normal by Sudan III

* Kindly performed by Dr. H. Schwachman, Children's Medical Center, Boston.

staining. The reaction to an oral glucose tolerance test was normal. A xylose absorption test showed a low urinary recovery of 2.6 gm. in five hours (normal 5 to 8 gm.). Amylase was present in normal amounts both in duodenal juice and in serum.

Adrenal cortical secretion, as shown in Table II and Figure 5, was normal or hyperactive. Twenty-four hour urinary excretion of 17-ketosteroids was initially low but there was a normal response to stimulation with intravenously administered ACTH [*11*]. Urinary excretion of 17-hydroxycorticosteroids was consistently elevated and showed a normal rise after stimulation with intravenously administered ACTH [*11*]. Eosinophil counts were persistently low, ranging from 25 to 106/cu. mm. In order to establish the rate of synthesis of hydrocortisone, a turnover study was performed by giving the patient an intravenous infusion of 100 mg. of unlabeled hydrocortisone over a thirty-minute period.* The half-life of seventy-six minutes was shorter than the normal values of 107 to 121 minutes previously reported [*12,13*], and indicated an increased rate of synthesis. Urinary aldosterone levels were high, ranging from 24 to 78 μg./twenty-four hours (normal 1 to 10 μg./twenty-four hours), and the urinary Na/K ratio was also reduced.

Chest roentgenograms revealed bilateral pleural effusions, elevated diaphragm, and areas of atelectasis but no cardiac enlargement. A roentgenogram of the abdomen showed ascites. Intravenous pyelograms disclosed kidneys of normal size and position, with poor concentration of dye bilaterally. Gastrointestinal motility study showed a rapid transit time of a half hour from stomach to cecum. The gastric mucosa appeared irregularly thickened and the intestinal mucosa also appeared thickened, with loss of structural detail and clumping of barium in some areas. No esophageal varices were seen. Barium enema was normal.

* Kindly performed by Dr. J. W. Meakin, Peter Bent Brigham Hospital, Boston.

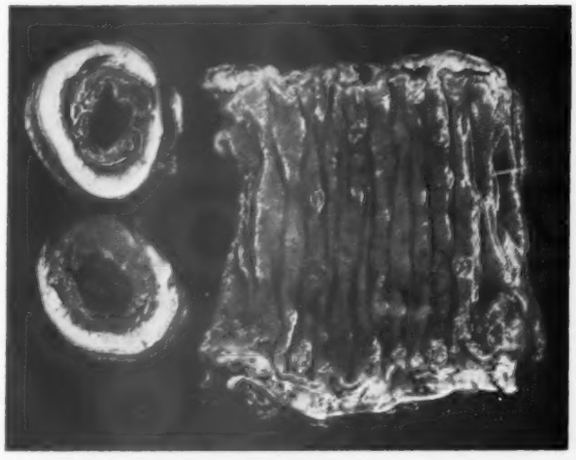


FIG. 6. Jejunum resected at laparotomy shows marked edema. Cross sections, at left, show thickening and edema of the entire wall. Specimen opened longitudinally shows thickened folds and prominent edematous villi.

There was no evidence of congestive heart failure as a cause of anasarca. Venous pressures taken simultaneously in the antecubital and femoral veins were 40 and 145 mm. of water, respectively. The slightly elevated femoral pressure was perhaps due to increased intra-abdominal pressure on the inferior vena cava as a result of ascites. The arm-to-tongue circulation time (Decholin®) was twelve seconds, and the vital capacity slightly reduced to 1.5 L. The electrocardiogram showed low voltage. The butanol-extractable iodine was 5 μg. per cent (normal 3.2 to 6.4 μg. per cent).

Biopsy material of the stomach and jejunum obtained at laparotomy is illustrated in Figure 6. Grossly the jejunal mucosal folds were thick and broad, with multiple fine and prominent villi. On microscopic examination the jejunal wall showed edema throughout, with large, edematous, occasionally club-shaped

TABLE II
ACTH TEST

Twenty-Four Hour Periods	17-Hydroxy-corticoids (mg./24 hr.)	17-Keto-steroids (mg./24 hr.)	Normal Values* (mg./24 hours)	
			17-Hydroxy-corticoids	17-Ketosteroids
Control day 1	16.2	4.8	4.8 (1.0 to 10.0)	18 (14 to 25)
Control day 2	21.6	5.5		
ACTH 25 units over 8 hours	49.2	13.4	14 (5 to 25)†	4 (0 to 8.3)†
ACTH 25 units over 8 hours	48.5	13.8	24 (15 to 41)†	6 (1.8 to 10.9)†
Day following the administration of ACTH	54.3	11.2		

* Normal values for males [*11*].
† Increment over the average control.

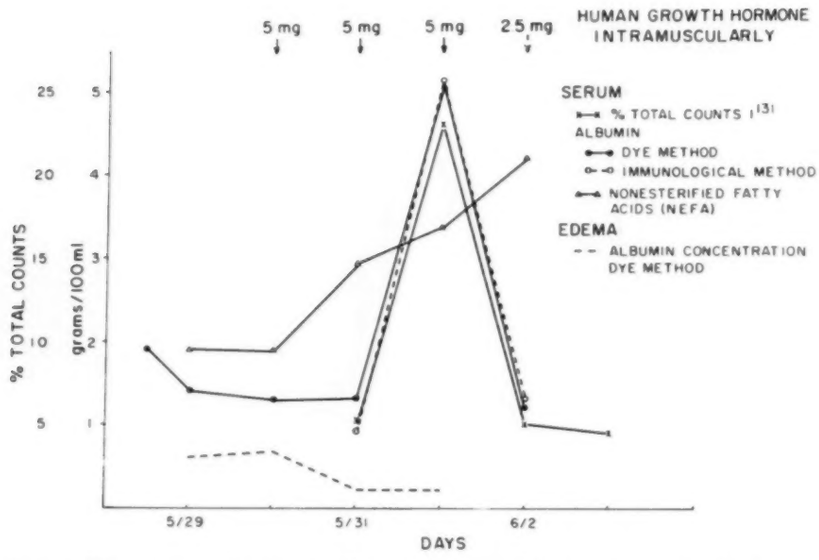


FIG. 7. The increase in serum albumin concentrations is illustrated by three technics: (1) per cent total counts of RISA; (2) immunologic method [*14*]; (3) dye-binding method [*15*]. Note the increase in serum albumin concentration concurrent with the decrease in edema fluid albumin concentration and the administration of human growth hormone. The rise in serum NEFA establishes the potency of the growth hormone.

villi and dilated lymphatics in the submucosa. There was moderate inflammatory cell infiltration of the mucosa with eosinophils, lymphocytes, plasma cells and a few neutrophils. There was no periodic acid-Schiff staining material in the macrophages to suggest Whipple's disease. The epithelium was intact. The gastric mucosa was normal on microscopic examination. Liver biopsy showed mild fatty metamorphosis of the parenchyma and increased fibrous tissue, leukocyte infiltration, and small bile duct proliferation in the portal areas. The ascitic fluid showed no tumor cells. A gingival biopsy revealed no evidence of amyloidosis. A bone marrow examination showed a moderate plasmacytosis, mostly of mature cells.

Hospital Course

Steroid therapy was instituted in the expectation that, if the hypercatabolism of serum albumin were due to hyperactivity of the reticuloendothelial system (RES), such therapy would inhibit RES activity and decrease the rate of catabolism. After most investigations had been completed, treatment was begun with ACTH (Fig. 5), which was given (40 units intramuscularly) for two days. Prednisone was then administered for several days (30 mg. daily orally), followed by a trial of cortisone (100 mg. daily orally). Prednisone and cortisone were given alternately for a four-week period without evidence of improvement. On the contrary, there was progressive deterioration as manifested by increasing anasarca, a persistently increased stool nitrogen, and a decreasing serum albumin concentration. Therapy with albumin (25 to 75 gm. daily given intravenously for two weeks) was tried next. (Fig. 2.)* This caused only a moderate increase in the serum albumin level (0.3 rising to 1.4 gm. per cent).

Progressive deterioration of the patient's clinical condition led to surgical exploration in the hope of finding a resectable lesion which was responsible for the leakage of serum proteins into the gut. On March 5, 1958, (twelfth hospital week), after intensive treatment with intravenously administered albumin to reduce intestinal edema, a laparotomy† revealed marked thickening and hypertrophy of the proximal jejunum, which demonstrated increased irritability and vascularization with prominent tortuous, arborizing vessels on the serosal surface. On cross section the mucosa and entire intestinal wall were markedly thickened. These changes extended to 6 feet below the ligament of Treitz and this segment was resected. The stomach, liver and colon were grossly normal. There was no portal hypertension (portal pressure 120 mm. water) and the peritoneum showed no apparent abnormality. Histological examination of stomach, liver and small bowel showed predominantly edema of the jejunum, as already indicated.

The patient tolerated the laparotomy well and the postoperative period was uncomplicated except for

* Kindly supplied by the Protein Foundation, Jamaica Plain, Massachusetts, and the Department of Public Health, Massachusetts.

† This operation was performed by Dr. Francis D. Moore and his associates.

recurrent ascites which required frequent paracenteses. Because of the persistent ascites, a peritoneojugular shunt was performed on March 20, 1958 (fifteenth hospital week). Despite these extensive procedures the patient's clinical state did not improve. The anasarca persisted. The serum albumin and total protein rose while he received huge amounts of albumin intravenously (100 gm. daily for approximately two weeks) but never reached normal levels. The stool nitrogen levels remained markedly elevated. Repeated radioactive albumin studies continued to show a shortened half-life.

The high concentration of albumin in edema fluid relative to the serum albumin concentration and the loss of serum proteins into the gastrointestinal tract suggested that a diffuse increase in peripheral capillary permeability might be partly responsible for the severe hypoalbuminemia. Growth hormone was given in an attempt to stimulate connective tissue formation and to diminish the abnormal capillary permeability. The patient received 2.5 mg. of human growth hormone* intramuscularly twice daily for three days (seven doses). On the third day of therapy there was a marked increase in the concentration of serum albumin, which rose from 1.3 to 5.1 gm. per cent in a period of twenty-four hours, and a corresponding fall in the edema fluid albumin concentration from 640 to 220 mg. per cent. (Fig. 7.) There was a corresponding fourfold increase in the amount of radioactive albumin-I^{131} in the serum. (Fig. 8.) The patient's weight was stable during these changes in albumin distribution. The increase in serum albumin was transient, however, and fell to pretreatment levels on the fourth day. The potency of the growth hormone preparation was confirmed by the progressive rise of serum non-esterified fatty acids, as shown in Figure 7.

Shortly after these studies pulmonary edema and peritonitis developed. The patient died on June 6, 1958, in his twenty-fourth hospital week.

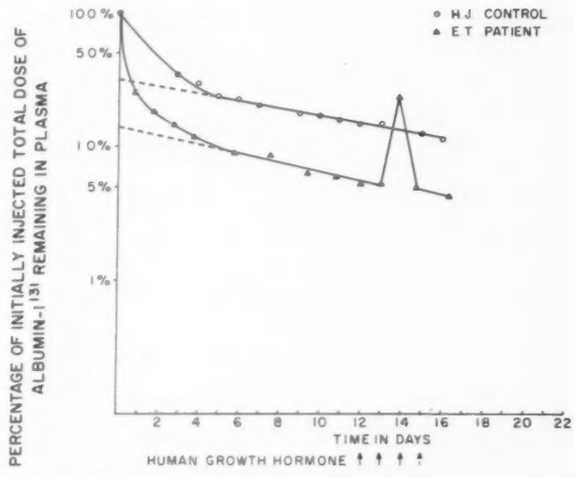


FIG. 8. Effect of human growth hormone on serum albumin. On the third day of growth hormone administration a transient fourfold increase in the concentration of radioactive albumin occurred in the intravascular (plasma) compartment.

Postmortem Examination

There was generalized anasarca with 200 ml. of clear amber fluid in each pleural cavity. The lungs were hyperemic, with microscopic edema and bronchopneumonia. There were thrombi with bacterial colonies in some of the small pulmonary arteries. The right femoral vein was thrombosed and showed early organization. The peritoneal cavity contained 1,500 ml. of thick greenish yellow fluid which was loculated in some areas. The peritoneum was covered by a rough adherent gray-white membrane. The subcutaneous catheter forming the peritoneojugular shunt was thrombosed. The jejunal anastomosis was intact and no defect in the gastrointestinal wall could be detected.

The stomach showed minimal polypoid hyperplasia at the pylorus, the duodenum exhibited a similar prominence of the mucosa. There was minimal infiltration of the pylorus by lymphocytes and plasma cells. In the duodenum there was a moderate increase in the papillary character of the plical folds, with thickening of the lamina propria and infiltration by plasma cells and lymphocytes. The submucosa was thickened and contained dilated lymphatic vessels. The muscularis appeared normal. The serosa and subserosa were markedly thickened by edematous fibrous connective tissue infiltrated by numerous neutrophils, lymphocytes, eosinophils and macrophages. On the serosal surface there were adherent patches of neutrophils and fibrin showing early organization. The jejunum and ileum were similar in appearance and showed edema of the submucosa. The lamina propria of the colon was edematous, with dilated lymphatics.

The liver weighed 2,900 gm. and had a firm tan parenchyma with slight prominence of the portal areas. Microscopically there was moderate distortion of the lobular pattern by fibrous trabeculae extending between portal areas which contained proliferating bile ducts and lymphocytic infiltration. The nuclei of the hepatic cells varied in size and staining characteristics. The cytoplasm was occasionally vacuolated. The spleen weighed 350 gm. and showed a normal distribution of lymphoid follicles. There was diffuse infiltration of the parenchyma by plasma cells and hyperplasia of the cells lining sinusoids. The right kidney weighed 140 gm., the left 180 gm. No significant abnormalities were evident on gross or microscopic examination.

The right adrenal gland weighed 10 gm., the left 12 gm. The cut surface was normal in appearance. There was diffuse thickening of the cortices, predominantly in the zona fascicularis, with small narrow

* Kindly supplied by Dr. Maurice Raben, Tufts University Medical School, Boston.

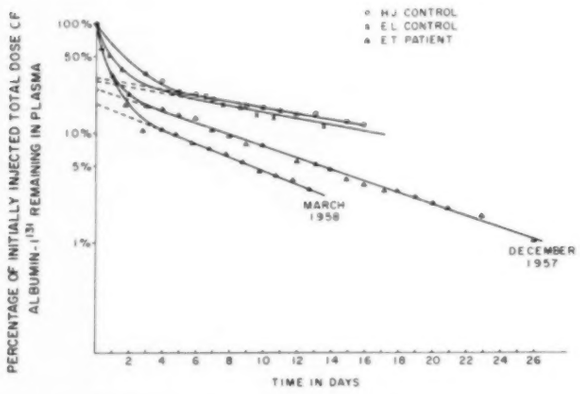


FIG. 9. Plasma disappearance curves. Symbol represents two turnover studies on patient (E. T.) using different lots of albumin-I^{131} (RISA) for each study. Symbol "X" represents turnover study on control subject (E. L.) performed with the same lot of RISA as used in the March, 1958, turnover study of our patient (E. T.). Symbol "O" represents a control turnover study with a different lot of RISA. The following points are noteworthy: (1) The two control turnover studies show approximately normal half-lives of 10.5 (E. L.) and 11 (H. J.) days. (2) The two turnover studies on the patient (E. T.) show shortened half-lives of 5.7 and 4.9 days.

layers of glomerulosa and reticularis. The cortical cells were pink-staining, with some vacuolation and pigmentation. Small focal areas of degenerated cortical cells with dense inflammatory cell infiltration were scattered throughout the cortex. The medulla was normal. The pituitary gland weighed 400 mg. and appeared grossly normal but microscopy revealed infarction with loss of cellular and nuclear detail in approximately a third of the anterior pituitary. There was little cellular reaction or attempt at organization in the surrounding tissue.

The heart appeared normal on gross examination. Microscopic examination showed focal areas of fibrosis and a few areas of necrosis with neutrophilic infiltration. The bone marrow showed normal hematopoiesis except for a moderate increase in the number of plasma cells in varying stages of maturity. In the lymph nodes there were increased numbers of reticuloendothelial cells in discrete cords, edematous lymphoid tissue and diffuse infiltration by plasma cells in varying stages of maturity. The skin showed spaces between the collagen fibers which were suggestive of edema. A few foci of perivascular infiltration by lymphocytes, plasma cells and eosinophils were present about dermal blood vessels. The subcutaneous fat contained a few shrunken fat cells with thickened walls. The pancreas, thyroid, parathyroids and brain were normal on gross and microscopic examination.

Culture of heart blood grew Aerobacter aerogenes. Culture of the peritoneal fluid grew Aerobacter aerogenes, Proteus vulgaris, beta hemolytic enterococci and Staphylococcus aureus.

RADIOACTIVE ALBUMIN-I^{131} TURNOVER STUDIES

Since hypoalbuminemia in this patient may have reflected decreased synthesis, increased catabolism, external loss, or abnormal distribution within various body compartments, a turnover study using a tracer dose of albumin labeled with radioactive iodine (I^{131}) was performed on two occasions, by a method previously described [*2*]. Radioactive albumin was supplied by Abbott Laboratories as RISA (radioiodinated serum albumin).

Two control subjects also received the same lots of albumin-I^{131} (RISA) used in this study. One of these control subjects was recovering from a myocardial infarction without congestive heart failure. The other had chronic pulmonary disease. Both were considered to have relatively normal protein metabolism.

The two turnover studies, each with a different lot of albumin-I^{131} (RISA), resulted in a shortened half-life of 4.9 and 5.7 days (average 5.3). In the control subjects the half-life was 10.5 and 11 days (average 10.8). The control values were at the lower limits of normal for the majority of patients in our previous experience and in the literature, in which the half-life is generally stated to range from eleven to seventeen days for Abbott RISA [*16*]. The underlying disease processes in the control subjects may have increased their rates of protein metabolism more dynamically than was apparent from the normal serum albumin measurements alone. Indeed, one subject (E. L.), although apparently well and discharged from the hospital during the turnover study, died abruptly at its termination of a myocardial infarction.

The graphs depicting the plasma disappearance of albumin-I^{131} are shown in Figure 9. There are two components to each curve. The first component with a steep slope represents three possible physiological phenomena occurring simultaneously: distribution, catabolism and external loss. The straight-line portion of the curve represents only catabolism and external loss (if there is any), once equilibrium has been established between the intravascular and extravascular compartments. The half-life of albumin-I^{131} is defined as the time (in days) for half of a given number of labeled molecules to disappear and is estimated from the straight-line portion of the curve.

Knowing the half-life, one can calculate the fractional rate of turnover (catabolism plus ex-

ternal loss, if any) of albumin. The fractional rate of turnover (F.R.T.) is defined as the percentage of the body pool of albumin being removed from the body by catabolism and loss per day. Using values averaged from the two turnover studies in the patient (E. T.), the F.R.T. can be calculated by the following equation [*16*]:

$$\text{F.R.T.} = \frac{\ln 2}{T\,\frac{1}{2}} = \frac{0.693}{5.3 \text{ days}} = 0.131 \times 100 = 13.1 \text{ per cent per day}$$

By contrast, in the two control subjects (taking a half-life value averaged from both turnover studies),

$$\text{F.R.T.} = \frac{0.693}{10.8} = 0.064 \times 100 = 6.4 \text{ per cent per day}$$

Knowing the fractional rate of turnover, the *amount* of albumin removed each day can be determined by measuring the total body pool of albumin (Talbumin). This total albumin pool consists of the intravascular and extravascular pools. The intravascular or plasma pool may be calculated by measuring the plasma concentration and the plasma volume.

$$\text{plasma albumin concentration } \frac{(\text{gm.})}{(\text{L.})} \times \text{plasma volume (L.)} = \text{total plasma albumin (gm.)}.$$

$$5.75 \frac{\text{gm.}}{\text{L.}} \times 3.7 \text{ L.} = 21.3 \text{ gm. albumin}$$

Plasma volume is determined by isotope dilution at the time of injection of RISA, assuming that complete plasma distribution and negligible extravascular diffusion occurs within twelve minutes after intravenous injection. By contrast, the normal subject (H. J.) had a plasma albumin concentration of 40 $\frac{\text{gm.}}{\text{L.}}$ × plasma volume of 3.44 L., or 138 gm. of albumin in the intravascular compartment.

The *extravascular pool* may be calculated from the following information. In an edematous patient the interstitial fluid (I.S.F.) concentration of albumin can be measured directly since a sample can be obtained via a needle placed subcutaneously in the leg. In our subject (E. T.), the concentration was 175 mg. per cent. The volume of edema fluid was estimated by taking the difference between his normal weight and his edematous weight (16 kg.). Normal interstitial fluid volume was estimated to be three times the plasma volume (11.1 L.). Therefore total interstitial fluid was obtained by adding these two values together.

$$\text{Total interstitial fluid} = \text{normal I.S.F.} + \text{edema} = 11.1 \text{ L.} + 16 \text{ L.} = 27.1 \text{ L.}$$

$$(E_{albumin}) = 1.75 \frac{\text{gm.}}{\text{L.}} \times 27.1 \text{ L. (I.S.F.)} = 47.4 \text{ gm.}$$

$$(T_{albumin}) = \text{plasma}_{albumin} + E_{albumin} = 21.3 + 47.4 = 68.7 \text{ gm.}$$

Direct I.S.F. albumin measurements were not possible in our control subject but an estimation can be made. Extrapolation of the straight-line portion of the plasma disappearance curve (Fig. 9) back to the time of injection (zero time) indicates the percentage of the total body pool of albumin which would have been present in the plasma if distribution into the extravascular space had occurred instantly after injection with the immediate establishment of equilibrium. In our control subject (H. J.), it was 34 per cent of the total injected dose, a value slightly lower than the usual observation that 40 to 45 per cent of the total body pool of albumin is intravascular and 55 to 60 per cent extravascular [*17,18*]. Since the control subject's (H. J.) intravascular albumin pool was 138 gm.,

$$T_{albumin} \times 0.34 = 138 \text{ gm.}$$

$$\therefore T_{albumin} = \frac{138 \text{ gm.}}{0.34} = 406 \text{ gm.}$$

Knowing both the total albumin pool and the fractional rate of turnover, it is possible to calculate the amount of albumin catabolized and lost per day.

$$\text{F.R.T.} \times T_{albumin} = \text{total amount of albumin removed per day}$$

$$0.131 \times 68.7 \text{ gm.} = 9.0 \text{ gm. in patient (E. T.)}$$

$$0.064 \times 406 \text{ gm.} = 26.0 \text{ gm. in control subject (H. J.)}$$

Since the patient was in a steady state with respect to protein metabolism, the serum albumin neither rising nor falling, the amount synthesized must be considered equal to the amount catabolized per day.

Therefore, albumin catabolism (and loss, if any) = albumin synthesis per day

9.0 gm. = 9.0 gm. in patient (E. T.)
26.0 gm. = 26.0 gm. in control subject (H. J.)

Since the synthesis of albumin in normal subjects ranges from 15 to 25 gm. per day, our patient (E. T.) had a reduced rate of synthesis, while the control subject (H. J.) had a slightly increased rate of synthesis [*19*].

POSSIBLE INTERPRETATIONS OF AN INCREASED FRACTIONAL RATE OF TURNOVER

An accelerated plasma disappearance of albumin-I^{131} may be caused by faulty preparation of the labeled albumin, external loss, an increased fractional rate of catabolism or a combination of these factors. Denaturation of proteins accelerates their removal from the blood stream. Denaturation of labeled albumin preparations may occur methodologically as a result of harsh treatment during the isolation of the albumin fraction, overiodination (i.e., tagging with more than ten iodine molecules per molecule of albumin) [*20*], heat treatment of the albumin for sterilization [*21*], or internal radiation damage [*22*]. Until recently even carefully labeled proteins had somewhat shorter half-lives than unlabeled protein preparations injected into the same patient, as observed in patients with agammaglobulinemia and analbuminemia studied with both labeled and unlabeled preparations of their specifically deficient plasma protein fractions [*17*]. This difficulty may be obviated by newly developed technics of iodinating proteins [*23*], which yielded identical half-lives for labeled and unlabeled albumin in a patient with analbuminemia [*24,25*]. Nevertheless, although values for rates of synthesis and catabolism may not have absolute validity, these studies with labeled plasma proteins have relative validity, allowing comparison of normal and abnormal rates so long as normal control subjects are used to test the integrity of a given labeled plasma protein preparation.

GASTROINTESTINAL EXUDATION

Once methodological considerations have been excluded, a shortened plasma disappearance curve suggests either hypercatabolism or external loss, or both. No distinction between these phenomena can be made from the plasma disappearance curve. One must find the source of the external loss to implicate this mechanism. The patient did not have obvious sources of external loss such as proteinuria or an exudative skin lesion. The demonstration of serum albumin and three globulins in the gastric and jejunal juices by qualitative immunological technics led to an attempt to quantify the contribution of intestinal exudation to the total amount of hypercatabolism. Several days after the intravenous injection of radioactive albumin, gastric and duodenal juices were aspirated over a six-hour period and a four-day stool specimen was collected. These specimens were assayed for albumin-bound I^{131}. Total I^{131} activity was not considered significant information because of the active secretion of HI^{131} (in place of HCl) in the stomach. It was calculated that the stomach exuded 0.6 gm. of albumin per twenty-four hours. Larger amounts of albumin were found in the duodenum, amounting to at least 2.6 gm. per twenty-four hours, or a fractional rate of turnover of 3.5 per cent per day. If this were an accurate value, catabolism without intestinal exudation could be calculated by subtracting the contribution of duodenal albumin catabolism (3.5 per cent per day) from the total fractional rate of turnover (13.1 per cent per day), which is 9.6 per cent per day. This value of 9.6 per cent per day is still significantly higher than the normal fractional rate of catabolism, which in our control subjects was 6.4 per cent, and would imply that hypercatabolism was also occurring somewhere in the body other than the gastrointestinal tract. This may or may not be true. It must be emphasized that the value of 3.5 per cent per day for the fractional rate of catabolism attributed to duodenal exudation is a *minimal* value. It is likely that some exuded duodenal albumin-I^{131} was hydrolyzed into tyrosine-I^{131} residues by proteolytic enzymes and escaped detection as protein-bound I^{131}. These residues may be reabsorbed into the bloodstream and reexcreted into the urine, leading to the erroneous impression that catabolism had occurred elsewhere in the body. In fact, when the urinary excretion of I^{131} (representing catabolized albumin-I^{131}) is calculated by the method of Berson et al. [*20*] it is found that catabolism occurs in the extravascular as well as the intravascular space. This is in contrast to other

hypercatabolic conditions without gastrointestinal exudation and also in contrast to normal subjects in whom catabolism presumably occurs in the intravascular compartment alone [*26*]. Moreover, it appears likely that albumin was exuded into other parts of the intestinal tract as well, particularly the jejunum, in which albumin was demonstrated qualitatively. Although albumin was found in the stomach (0.6 gm. per day), it was not included in these calculations on the conservative assumption that all of it might have appeared as albumin-I^{131} before hydrolysis in the duodenal juice. If this assumption were not true, it would argue further for the role of exudation in accounting for the total fractional rate of turnover (i.e., catabolism). The presence of only minimal amounts of albumin-I^{131} in the four day stool collection (0.2 gm.) bears little weight against this thesis because enzymatic hydrolysis results in subsequent reabsorption of the amino acid residues, not fecal excretion. The elevated stool nitrogen values indicated the excretion of 12 to 18 gm. of protein (above normal values) which could not be accounted for by impaired absorption and may have been due to exuded plasma proteins. In the light of these considerations, it seems probable that if sufficiently complete collections of the intestinal fluids had been made the increased fractional rate of albumin turnover might be explained in terms of a normal fractional rate of catabolism (wherever it normally occurs) plus exudation into the gastrointestinal tract with additional catabolism there.

COMMENTS

Idiopathic hypoalbuminemia resulting in edema, without dietary protein deficiency and without evident cardiac, hepatic, intestinal or renal disease, has been a recognized clinical entity since early in this century. Under the clinical description of "idiopathic hypoproteinemia" over fifty cases have been reported [*27–64*]. Knowledge of the physiological dynamics responsible for hypoalbuminemia has made rapid strides during the last two decades. Clinical observation has long implicated the liver as the source of albumin synthesis and more recent studies on isolated perfused rat livers with isotopic amino acids have confirmed these impressions [*65,66*]. Pathophysiological investigations on dogs by Whipple and his associates [*67*] since the 1930's have shown that there is a sizable plasma protein pool in the extravascular as well as intravascular compartment.

The mechanism of "idiopathic hypoproteinemia" in human beings was first intensively studied in the middle 1940's by Albright who infused large amounts of human albumin intravenously into an individual with the disease and found by meticulous balance studies that it was catabolized at an increased rate [*45*]. Albumin labeled with radioactive isotopes was introduced in the late 1940's and simplified dynamic studies. In 1950 Kinsell [*49*] (using S^{35} labeled plasma proteins) and in 1957 Schwartz and Thomsen [*58*] (using albumin-I^{131}) performed turnover studies in three patients with "idiopathic hypoproteinemia" and concluded that an increased rate of degradation was the physiological derangement. The latter authors suggested the name "idiopathic hypercatabolic hypoproteinemia." In 1959 Gordon introduced the use of polyvinyl pyrrolidone-I^{131} (PVP-I^{131}), a dextran polymer of molecular weight averaging about 40,000 (albumin is 66,000) which is not hydrolyzed by intestinal proteolytic enzymes, and showed that after intravenous injection more than the normal amount of 1.5 per cent of the injected dose could be found in a four-day stool collection of nine patients with "idiopathic hypercatabolic hypoproteinemia" [*63*]. This finding was confirmed in an additional four patients by Schwartz and Jarnum [*64*]. Gordon concluded that "idiopathic hypercatabolic hypoproteinemia" resulted from an abnormal leakage of plasma proteins into the gastrointestinal tract, such as may occur in giant hypertrophy of the gastric mucosa [*68*], sprue [*64*], regional ileitis [*69*] and chronic ulcerative colitis [*69*]. He suggested the name "exudative gastroenteropathy."

The Meaning of Hypercatabolism. Hypercatabolism refers to an increase in the fractional rate of catabolism (i.e., percentage of the body pool catabolized per day) and is reflected by a shortened half-life of the labeled albumin. It does not refer to the amount of albumin, as measured in grams, catabolized per day. Indeed, when the total body albumin pool is markedly reduced in certain hypercatabolic states, the *amount* of albumin catabolized per day may be less than normal. For example, our patient (E. T.) catabolized only 9.0 gm. of albumin per day, whereas the normal range is 15 to 25 gm. per day. Yet, this was an abnormally increased percentage of his total body albumin pool (13.1 per cent) compared to normal (4 to 6 per cent).

The validity of this concept is based on the knowledge that plasma proteins are subject to

the laws of a first order reaction. Catabolism removes a relatively fixed fraction or percentage of the total body pool of albumin each day, not a fixed number of molecules [*17*]. When the total body albumin pool is reduced, as occurs in malnutrition [*70*] or after plasmapheresis [*71*], the fractional rate of catabolism remains relatively stable. In fact, in hypoalbuminemia due to Laennec's cirrhosis [*11*], congestive heart failure with proteinuria [*72*] or chronic renal disease with proteinuria [*73*], the fractional rate of catabolism may actually decrease. By contrast, in hypercatabolic conditions, such as idiopathic hypercatabolic hypoproteinemia and severe nephrosis of childhood, the fractional rate of catabolism increases [*2*].

Mechanisms of Hypercatabolism. Gastrointestinal exudation of plasma proteins may occur, producing an increased fractional rate of catabolism. The presence of albumin and three plasma globulins in the jejunal juice, and of albumin in the gastric and duodenal juice of our patient (E. T.) demonstrated this route of catabolism. Quantitatively, it appeared likely that most if not all of the entire increase in the fractional rate of catabolism was due to gastrointestinal exudation, but for methodological reasons this could not be definitely proved. The pathway of exudation into the gastrointestinal tract was not ascertained. The widespread exudation in stomach, duodenum and jejunum suggested a diffuse process, which may have resulted from the generalized increase in peripheral capillary permeability.

Adrenal cortex hyperactivity may also have played a role in the pathogenesis of the hypoalbuminemia. Rothschild et al. [*74*] have shown that cortisone and hydrocortisone may increase the fractional rate of catabolism of albumin, although this is compensated for by increased albumin synthesis in normal subjects. The persistently high serum levels and increased rate of synthesis of 17-hydroxycorticoids in our patient (E. T.) may have contributed to his increased fractional rate of albumin catabolism.

Other pathophysiological mechanisms implicated in hypercatabolic states are hyperthyroidism [*75*], and a hypersensitivity reaction to pooled infused albumin [*76*]. Thyrotoxicosis was ruled out by the normal parameters of thyroid activity. Precipitins in the patient's serum against normal human pooled albumin (Cohn fraction v) were absent by the ring test, making a hypersensitivity mechanism appear unlikely. Physicochemical abnormalities of the patient's native albumin resulting in increased rates of degradation were not investigated but are interesting possibilities in view of the discovery of "molecular" diseases [*77*].

Sites of Catabolism. The normal site or sites of catabolism in man are not known. In mice, catabolism predominantly occurs in the reticuloendothelial system, particularly of the liver and spleen, and in the kidneys [*78*]. In rats the liver accounts for up to a half of the fractional rate of catabolism [*79*]. In neither animal is the intestine thought to play a significant role in normal catabolism. In our patient (E. T.), however, in whom intestinal exudation was a highly significant factor, an abnormal physiologic state was present with increased peripheral capillary permeability, which may have provided a large number of portals for plasma proteins to escape into the gut. Unfortunately, electron microscopic studies were not made on the intestinal mucosa to determine whether or not some abnormal permeability existed in this barrier.

Plasma Protein Changes in Hypercatabolism. Hypercatabolism in the nephrotic syndrome affects not only albumin but also gamma globulin, iron-binding globulin [*2*] and probably ceruloplasmin [*80*]. One feature common to these plasma proteins is a molecular weight below 160,000. In our patient (E. T.) three of these four proteins (all except gamma globulin) were reduced markedly below normal concentrations. Since a turnover study was performed on albumin alone, hypercatabolism can be clearly implicated only for this plasma protein as an explanation for the low exchangeable body pool. It seems likely that hypercatabolism was also responsible for lowering the serum concentrations of iron-binding globulin and ceruloplasmin as well, particularly since other plasma proteins (globulins) were found in the intestinal tract. However, impaired hepatic synthesis of albumin also coexisted with hypercatabolism and hypoanabolism may have been partly or entirely responsible for the low body pools of these other proteins. Still another possible contributing factor is the effect of the albumin infusions, which may have caused a significant fall in the concentration of serum iron-binding globulin [*81*].

The relatively normal and at times even increased serum concentration of gamma globulin, which is usually reduced in hypercatabolic states, may be explained by a high rate of synthesis. The gamma globulins are the only major group of plasma proteins synthesized inde-

pendently of the liver and therefore would not have been victims of impaired hepatic anabolic activity. Since they are formed by plasma cells, the presence of an increased number of plasma cells in the patient's bone marrow, spleen and lymph nodes, such as occurs in many hypergammaglobulinemic states, suggested the possibility of an increased rate of synthesis. Indeed, the combination of increased plasma cell counts and a narrow, peaked elevation of a segment of the gamma globulins on starch gel electrophoresis suggested the diagnosis of early multiple myeloma. In multiple myeloma, in which there may be abnormal increase of a gamma globulin component, dynamic studies indicate that amino acids may be diverted from albumin synthesis to the synthesis of the abnormal gamma globulin, resulting in hypoalbuminemia [*82*].

Although the lower molecular weight plasma proteins have low serum concentrations and an increased rate of degradation with normal or increased rates of synthesis in the hypercatabolic conditions, the high molecular weight proteins are present in high serum concentrations, presumably due to increased synthesis. In our patient (E. T.) increased lipoprotein concentration was indicated by his elevated serum cholesterol level. Early in the course of disease he had lactescent serum, suggesting that the elevation was predominantly of the low density lipoproteins ($S_f > 400$) of molecular weight over 25 million [*83*]. Later in the course of the disease the elevated serum cholesterol levels occurred with clear serum, suggesting increased levels of the higher density lipoproteins. This elevated serum cholesterol is of particular interest because Wuhrmann and Wunderly [*84*] state that hypercholesterolemia does not occur in idiopathic hypoproteinemia. The elevation of the alpha$_2$-globulins was thought to be due predominantly to the macroglobulins (molecular weight of about 1 million) in this fraction [*85*] because it was markedly reduced in concentration after electrophoresis in starch gel. The starch gel medium has a molecular sieving effect which inhibits the migration of high molecular weight proteins [*86*]. Unfortunately a fibrinogen level (molecular weight 500,000) was not determined. The increased erythrocyte sedimentation rate may have been due either to an increase in fibrinogen (and possibly other globulins) or a decrease in the albumin concentration [*87*].

The mechanism of increased synthesis is unknown. It is significant that serum cholesterol levels in general rose to their highest levels after the serum albumin had fallen to its lowest levels. Raising the serum albumin concentration with intravenous albumin infusions lowered the cholesterol concentration. Late in the disease process, however, the serum cholesterol levels did not rise as strikingly in response to low serum albumin. This may have been due to a terminal hypoanabolic response of the liver resulting in diminished lipoprotein synthesis.

Hypoanabolism. The patient's rate of synthesis of albumin was considered to be reduced (9 gm. per day) below normal (15 to 25 gm. per day), based on calculations of his total body albumin pool and his fractional rate of turnover (catabolism plus exudation). Of critical importance in this calculation is the estimation of total body albumin. Immunological determinations make albumin measurements much more accurate at low concentrations in serum and edema fluids than can be achieved by other methods. Nevertheless, there are other possible methodological errors which must be considered. Because the patient had increased capillary permeability, his plasma volume may have been overestimated due to increased leakage of albumin-I^{131} across the capillary barrier. This would tend to overestimate the amount of albumin in the intravascular space. On the other hand, the amount of albumin in the extravascular space may have been somewhat underestimated because the albumin concentration in the interstitial fluid (edema) may have been lower than the average for all the separate, individual compartments within the extravascular space as a whole. For example, skin [*88*] and ascitic fluid [*2*] may have higher albumin concentrations than interstitial edema fluid. These calculations, nevertheless, are considered to be qualitatively valid, although the quantitative estimation of the degree of impaired albumin anabolism may be somewhat in error. If the patient had had a normal rate of synthesis of 18 gm. albumin per day, his total body pool of albumin would have fallen only to 137 gm., not 69 gm., even with an increased fraction rate of catabolism of 13.1 per cent per day. (Calculation: $T_{albumin} \times 0.131 = 18$ gm.; $\therefore T_{albumin} = 137$ gm.) Indeed many subjects under the stress of albumin loss or hypercatabolism are able to increase their rate of synthesis up to 50 per cent [*19*]. For example, in the patient's case, it should have risen from 18 to 27 gm. per day.

Since albumin is synthesized entirely by the liver, it is interesting that the patient's liver showed only mild fatty change and mild fibrosis

on histological examination. Moreover, there were no other biochemical abnormalities of hepatic parenchymal function, as estimated by serum bilirubin, prothrombin and alkaline phosphatase tests. Hypoanabolism of albumin has been observed as a single presenting feature, however, without biochemical or histological abnormalities in other patients with a history of alcoholism [*89*]. Decreased synthesis has also been noted in advanced Laennec's cirrhosis [*1,19*], in severe malnutrition [*70*] and in certain adult cases of the nephrotic syndrome [*90*].

Whether or not the low androgenic steroid levels played a significant role in producing hypoanabolism is unclear. Although the 17-ketosteroids did show a normal brisk rise after intravenous ACTH testing, secondary selective adrenal hypofunction may have existed due to a deficiency of pituitary function.

Increased Peripheral Capillary Permeability. Although interstitial fluid (I.S.F.) is not available for direct sampling in human beings without edema, it has been inferred from the distribution of albumin-I^{131} that approximately 55 to 60 per cent of the total body albumin pool is in the extravascular space. Most of this is presumed to be in the interstitial fluids, although some albumin can be demonstrated to be located intracellularly [*91*]. Assuming that the normal interstitial fluid volume is three times the plasma volume (i.e., 12 per cent and 4 per cent of the body weight, respectively), the average concentration of albumin in the interstitial fluid is approximately 30 per cent of the serum concentration. In edematous states the interstitial fluid volume (including ascites) may double or triple, as virtually occurred in our patient whose weight increased 16 kg. due to the accumulation of edema fluid. In most diseases associated with edema the percentage of the total albumin in each compartment remains approximately the same. As a result, the albumin concentration in the interstitial fluid may fall to one-third of its normal concentration (i.e., to one-tenth of the serum level [*92*]). In the nephrotic syndrome, it may fall to one-hundredth the serum albumin level, which itself is markedly depressed, for reasons which cannot be explained by dilution alone [*2*].

The remarkable finding in our patient was that the edema fluid albumin concentration (175 mg. per cent) was one-third of his serum albumin level (575 mg. per cent) despite an almost threefold expansion of his interstitial fluid volume. It is possible to explain this without assuming the presence of increased capillary permeability by postulating that a fixed amount of albumin might be held preferentially in the extravascular compartment despite a reduction in the total body albumin pool. Although knowledge of edema fluid albumin concentrations is not extensive, this postulate does not fit the available data or previous experience [*92*]. For example, in a case of idiopathic hypoproteinemia with edema, the edema albumin was 0.2 gm. per cent when the serum albumin was 2.6 gm. per cent, a concentration one-thirteenth the serum concentration [*58*].

There are, moreover, other factors suggestive of increased peripheral capillary permeability. Distributional equilibration between intra- and extravascular compartments of albumin-I^{131} after intravenous injection was rapid. It was one and a half days as measured by the equilibrium time method [*93*], and three days as measured by the plasma disappearance curve [*18*], the former probably providing a more accurate value. Normally equilibration requires four to seven days and longer when ascites is present. Experiments with growth hormone provided further evidence suggestive of increased permeability. Normally there is a continuous, dynamic exchange of albumin between the intravascular and extravascular compartments. Between 50 and 100 per cent of the total intravascular pool of albumin diffuses across the capillary barrier each day into the extravascular compartment, and is balanced by the lymphatic return of an equal amount of albumin from the extravascular compartment [*94*]. The briskness of this exchange in our patient (E. T.) was shown not only by the rapid exodus of intravenously injected albumin-I^{131}, but also by the massive accumulation of albumin in the intravascular compartment after growth hormone had been given in the attempt to decrease capillary permeability. The patient's serum albumin concentration rose fourfold, from 1.3 to 5.1 gm. per cent, while simultaneously there was a reciprocal fall in the interstitial fluid albumin concentration from 640 to 220 mg. per cent. There was a corresponding fourfold increase in the serum albumin-I^{131} concentration and a fall in the interstitial fluid albumin-I^{131} concentration. These reciprocal changes in serum and interstitial fluid albumin concentrations with a relatively constant specific activity (i.e., ratio of albumin-I^{131} to native unlabeled albumin) in each compartment suggest a

redistribution of albumin, with rapid return via the lymphatics and trapping within the intravascular compartment due to decreased (perhaps even abnormally decreased) capillary permeability, rather than anabolism of new albumin. Evidence for the rapid recirculation of albumin and other serum proteins was further strengthened by a twofold rise in the serum ceruloplasmin to a normal level and by the observation of abnormally dilated submucosal lymphatic vessels in edematous areas without evidence of lymphatic obstruction in the surgical and postmortem jejunal specimens. Clinically, the sudden increase in serum albumin was reflected by the rapid onset of pulmonary edema. The decrease in capillary permeability, however, was only temporary. On the following day, both serum albumin and albumin-I^{131} concentrations fell precipitously to previous levels, more rapidly than after the initial intravenous injection, as if capillary permeability had again suddenly become as abnormally increased as it had been during the course of his illness.

Growth hormone was used in the attempt to reverse the increased capillary permeability because of its known power to stimulate production of fibroblasts [*95*], collagen [*96*] and mucopolysaccharides [*97*] in connective tissue. The potency of the preparation was demonstrated by the steady rise of serum non-esterified fatty acids. However, the temporary (twenty-four hour) reversal of increased permeability was based upon only one carefully double-checked simultaneous analysis of serum and edema fluids and must await further study before such a physiological action can be unreservedly accepted even as a transient phenomenon.

The pathogenesis of edema in our patient (E. T.) was complex. Since the discovery of the clinical syndrome of congenital analbuminemia, in which a serum albumin level of 25 mg. per cent may be associated with only moderate edema [*98*], the importance of even marked hypoalbuminemia alone in causing massive anasarca has been questioned. In our patient (E. T.) other factors undoubtedly played significant roles. The increased capillary permeability permitted leakage of plasma proteins into the interstitial fluids with a resultant increased colloid osmotic pressure and water retention in the extravascular space [*99*]. Adrenal hypercortical activity, with increased aldosterone and 17-hydroxycorticoid levels, also may have been important factors by acting to enhance sodium and water retention.

Finally, it is interesting that the extreme wasting of the patient's body musculature and the marked depletion of his body pool of albumin stand as a poignant reminder of Whipple's thesis that protein metabolism must be assessed in terms of a dynamic equilibrium between intravascular, interstitial and tissue proteins [*100*].

SUMMARY

1. A fifty-nine year old white man presented with a two and a half year history of unremitting hypoproteinemia and anasarca (idiopathic hypoproteinemia).

2. Hypoalbuminemia, as revealed by albumin-I^{131} turnover studies, may have resulted from at least four abnormal physiologic mechanisms: (a) hypercatabolism, as reflected by an increase in the fractional rate of catabolism; (b) exudation of albumin and other plasma proteins into the stomach, duodenum and jejunum, resulting in an increased stool nitrogen; (c) hypoanabolism of albumin without any other known biochemical abnormalities of hepatic parenchymal function; and (d) increased peripheral capillary permeability resulting in the distribution of an unusually large percentage of the total exchangeable albumin pool in the extravascular compartment.

3. The hypoproteinemia involved not only albumin but also iron-binding globulin and ceruloplasmin.

4. There were increased concentrations of serum lipoproteins, as reflected by an elevation of serum cholesterol, and of alpha$_2$-macroglobulins. The concentration of serum cholesterol varied inversely with the serum albumin concentration, decreasing toward normal levels as the albumin level increased toward normal levels.

5. The increased peripheral capillary permeability was transiently reversed by the administration of human growth hormone.

6. Adrenal cortical hyperactivity was present, reflected by an increased concentration and rate of synthesis of hydrocortisone, high urinary excretion of aldosterone, and adrenal cortical hyperplasia. The increased adrenocortical activity may have played a contributory role in enhancing the increased fractional catabolic rate of albumin and the severity of the patient's massive edema.

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The Mechanism of Hypoproteinemia in Patients with Regional Enteritis and Ulcerative Colitis*

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In their recently revised monograph on regional enteritis, Crohn and Yarnis [*1*] mention the occurrence of hypoproteinemia when involvement of the intestine is extensive. Hypoproteinemia has also been recorded by others in patients with regional enteritis [*2–5*] and ulcerative colitis [*5–11*]. The relationship of this deficiency to the underlying disease process has been a matter of interest. The association of hepatic disease with ulcerative colitis, in particular, has been noted [*9,10*], but surveys of groups of patients with established ulcerative colitis have shown that hypoproteinemia often occurs in the absence of demonstrable impairment of hepatic function, as judged by other criteria [*3,6,10*]. Perhaps the most common view has been that nutritional deficiencies due to malabsorption are responsible for the hypoproteinemia. Direct studies of absorption of amino acids and proteins in subjects with these diseases have revealed some changes [*12–14*], and hyperalimentation has been advocated as a therapeutic measure [*15*]. However, deliberate induction of severe nutritional deficiencies in healthy volunteers has been reported to produce only a slight reduction in levels of plasma protein [*16*]. Furthermore, as Turner [*17*] points out, significant failure of protein and amino acid absorption has been noted only rarely in regional enteritis, so that the nutritional deficiency theory of the etiology of the hypoproteinemia occurring so commonly in this disorder is not satisfactory.

In 1937, Welch, Adams and Wakefield [*18*], studying nitrogen balance in a patient with severe ulcerative colitis, observed that fecal nitrogen output was high and, in certain periods, exceeded the dietary nitrogen intake. Clearly, such a situation could not be the result of malabsorption alone, and these authors attributed their observation to "exudation" of proteins from the inflamed bowel wall. Protein loss from the diseased ulcerated intestinal mucosa had indeed been mentioned by several investigators as a likely cause for the hypoproteinemia in ulcerative colitis [*6,9,10*] and regional enteritis [*2,3*]. Lack of suitable methods, however, precluded measurement of the rate of this process more satisfactorily than performed by Welch and his collaborators. It should be apparent that a simple nitrogen balance cannot serve to measure loss of plasma proteins into the gastrointestinal tract, since many other nitrogenous constituents, including digestive secretions and desquamated epithelial elements, enter the lumen under normal circumstances and are largely reabsorbed [*19*].

Patients with hypoalbuminemia may have subnormal serum albumin levels because of an expanded plasma volume, redistribution of albumin between the intra- and extravascular spaces, or a true subnormal total body albumin as a result of decreased albumin synthesis or excess albumin catabolism or loss.

The purpose of the present studies was to estimate plasma volume, total body albumin and albumin synthesis or catabolism in patients with ulcerative colitis and regional enteritis.

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TABLE 1

CLINICAL AND LABORATORY DATA ON PATIENTS WITH ULCERATIVE COLITIS OR REGIONAL ENTERITIS COMPARED WITH NORMAL GROUP

Chart No.	Diagnosis	Evidence for Diagnosis	Age (yr.) and Sex	Duration of Disease (yr.)	Weight Loss, Time of Study (kg.)	Serum (gm. %)		Plasma Volume (ml./kg.)	Total Circulating Albumin (gm./kg.)	Total Exchangeable Albumin	$T_{1/2}$ of I^{131}-Albumin (days)	I^{131}-Albumin Degraded per Day (%)	Albumin Turnover (gm./kg. per day)
						Total Protein	Albumin						
014526	Ulcerative entero colitis	Biopsy, x-ray film	15, M	6	3.2*	5.9	2.4	48.7	1.17	3.58	6.0	11.5	0.41
015080	Ulcerative colitis	Proctoscopy, x-ray film	13, M	6	4.1	7.2	3.7	54.8	2.02	5.10	9.1	7.6	0.39
016083	Ulcerative colitis	x-ray film	33, M	6	33.6	5.8	2.4	60.0	1.44	4.62	9.0	7.7	0.36
016997	Regional enteritis	Biopsy colon, x-ray film	62, M	18	0	6.0	3.1	38.8	1.21	3.22	7.8	8.9	0.29
014544	Regional enteritis	Biopsy, x-ray film	60, M	10	13.6	5.3	2.3	60.3	1.39	2.84	7.3	9.5	0.27
014835	Regional enteritis	Biopsy, x-ray film	66, M	9	0	4.2	1.5	55.8	0.92	2.94	8.0	8.6	0.25
016829	Inactive regional enteritis	x-ray film	27, M	7	22.7	5.6	2.8	54.4	1.52	3.37	11.2	6.2	0.21
Normal control subjects (16)		...	...	...	...		3.9	40.5	1.53	4.23	14.4	4.8	0.20

* Represents actual weight loss from 69 pounds at age 9 to 62 pounds at age 15.

The results indicate that patients with advanced regional enteritis or ulcerative colitis have subnormal total body albumin stores. The reason for this depletion of albumin appears to be an increased rate of albumin degradation or loss rather than an impairment of albumin production. Indeed, since these patients appeared to be in a steady state when studied, it may be assumed that albumin synthesis paralleled degradation, and the rate of synthesis so calculated actually exceeded that found in normal subjects. A mechanism for the excessive loss will be suggested.

MATERIALS AND METHODS

In an effort to determine the frequency of hypoproteinemia in patients diagnosed as having regional enteritis or ulcerative colitis, the hospital records of Barnes Hospital, St. Louis, Missouri from the year 1945 to the year 1955 were surveyed. All subjects discharged as having either of these disorders were considered, and the records were examined for data on serum protein levels. These determinations were carried out in the routine laboratory by the method of Weichselbaum [*20*]. The lower limits of normal values for this laboratory are considered to be 6 and 3.5 gm. total protein and albumin, respectively.

A smaller number of patients with established diagnoses of regional enteritis or chronic non-specific ulcerative colitis were studied while hospitalized at the Clinical Center of the National Institutes of Health. Some of the pertinent clinical data are listed in Table 1. Following an initial period of diagnostic study, the patients were given Lugol's solution, 10 drops every eight hours, to block thyroidal accumulation of I^{131}, throughout the period of study.

With the patients supine and fasting, 100 μc. of I^{131} albumin (RISA-T3 or RISA-T4) [*28*] in 10 ml. of saline solution were administered intravenously from a calibrated syringe, the injection containing approximately 500 mg. of albumin. Blood samples were removed from the opposite arm without stasis at fifteen and thirty minutes at one, two, four, six, twelve, eighteen and twenty-four hours, and daily thereafter. Daily quantitative collections of urine and stool were obtained. All patients were weighed daily before breakfast. *In vivo* determinations of radioactivity over the thigh and thyroid were carried out twice weekly to ascertain that no thyroidal concentration of I^{131} was occurring. The diet was not held rigidly constant, although an effort was made by both patients and staff to avoid excessive fluctuations in protein and total caloric intake. The patients' weights remained constant during the period of study, except for one subject (Case No. 014835), who lost 22 pounds of fluid due to edema during the latter halt of the investigation. Serum albumin and total protein determinations were performed thrice weekly, employing a modification of the method of Rutstein, Ingenito and Reynolds [*21*] and the method of Gornall, Bardawill and David [*22*], respectively.

Radioactivity determinations in duplicate were carried out to a standard deviation of 2 per cent on all samples. One ml. samples of plasma were assayed in a thallium-activated sodium iodide well scintillation

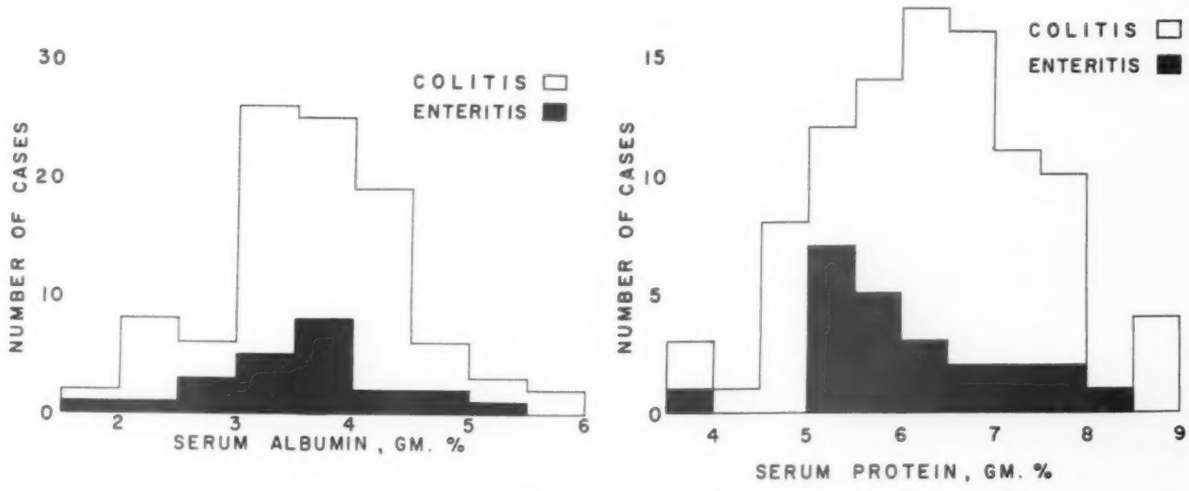


FIG. 1. Serum albumin (*left*) and serum protein (*right*) concentrations in patients with regional enteritis and ulcerative colitis. Lower limits of normal are 3.5 and 6.0 gm. per cent, respectively.

counter. One hundred ml. aliquots of urine and homogenized stool were counted over the crystal of the well scintillation counter. With each determination of radioactivity, an appropriate standard was also counted. These standards were prepared from sodium iodide^{131} solution on the day the study began, and were compared with the radioactivity of the I^{131}-albumin solutions administered to the patients. This procedure obviated errors that might occur due to the tendency of solutions of I^{131}-albumin to settle or adhere to the glass walls of containers during prolonged storage.

The results of the radioactivity determinations were plotted on semilogarithmic graph paper. (Fig. 1.) In each instance calculation of plasma and red cell volume was made by obtaining the extrapolated zero time value of plasma radioactivity and by using the following formulas:

$$\text{Plasma volume} = \frac{\text{Total activity administered}}{\text{Activity per ml. plasma at zero time (extrapolated)}}$$

$$\text{Blood volume} = \frac{\text{Plasma volume}}{1 - 0.91 \times \text{Peripheral venous hematocrit}}$$

$$\text{Red cell volume} = \text{blood volume} - \text{plasma volume}$$

Albumin turnover and total exchangeable albumin were estimated by isotope dilution according to the methods of Berson et al. [*23*], although in the measurement of total exchangeable albumin their method gives only an approximation [*24,25*]. The per cent of administered I^{131}-albumin remaining in the patient on any day is determined from the cumulative radioactivity excreted in the urine and stools on previous days. The logarithm of the per cent of the tracer remaining in the body is a linear function of time, following the equation $A_t = A_0e^{-kt}$ in which A_t is the amount of radioactivity remaining; A_0 is the initial injected radioactivity, 100 per cent; t is time, and k is the slope of the line. The $T_{½}$ is estimated for each patient, and k is determined by dividing 0.693 (ln 2) by the $T_{½}$. k is the fraction of the I^{131} remaining in the subject which is excreted each day. If one assumes that excretion of iodide^{131} is very rapid, compared to I^{131}-albumin degradation, the fraction of I^{131}-albumin catabolized each day is also given by k. Therefore, k may also be determined by dividing the total amount of radioactivity excreted on any day by the total amount still remaining in the subject on the mid-point of that day. The results of this calculation are expressed in the figures as "per cent IHSA degraded/day," which varies from day to day. Another variant of the isotope dilution technic for measurement of total exchangeable albumin is shown on the middle diagram of each chart. Here the concentration of radioactivity per ml. of plasma is multiplied by the plasma volume and divided by the total amount of radioactivity remaining in the body. When this curve reaches a horizontal asymptote, distribution is complete and the isotope dilution formula may be applied. Alternatively, plasma volume may be multiplied by albumin concentration to give a value for total circulating albumin. Then from the middle graph of each chart:

$$\text{Total exchangeable albumin} = \frac{100\% \times \text{total circulating albumin}}{\%\ \text{intravascular albumin}}$$

Polyvinylpyrrolidone (PVP) was labeled with I^{131} by a modification of the method of Ravin, Seligman and Fine [*26*], and dialyzed extensively, first with carrier iodide added, and then against running distilled water. It was made isotonic with dextrose, and prepared for intravenous injection by the pharmacy department, National Institute of Health Clinical Center. The starting material was a sample of PVP K-30 that had been refined for use as a blood volume expander. A few of the most recent tests were made with I^{131}-PVP prepared by a new method developed in this laboratory [*27*]. Each subject received 10 to 25 μc. of radioactivity intravenously, after having received sufficient iodide to prevent thyroidal uptake of I^{131}. This latter precaution was necessary because the polymer iodinated by the method of Ravin, Seligman and Fine [*26*] is subject to partial deiodination *in vivo*. Samples of plasma or whole blood were taken at suitable intervals, and each subject collected four twenty-four-hour urine samples and one cumulative ninety-six-hour stool sample from the time of the injection. Urine and blood radioactivity was determined by counting 3 ml. aliquots in a well-type scintillation counter. The stool samples were deposited in empty gallon size paint cans and, when complete, were each brought to a standard total weight by the addition of water. Approximately 20 gm. of phenol were added to each, and the matter homogenized within the sealed can by agitation. Each can then was assayed for radioactivity by placing it over the crystal of a scintillation probe, and the activity compared with that of a known aliquot of the labeled PVP solution distributed in a similar volume and container.

The patients who participated in this study were in many cases the same persons in whom I^{131}-albumin turnover studies were made. In addition, there were several other patients, similarly selected, who had only the PVP excretion test. The "normals" for comparison consisted primarily of patients with a variety of circulatory or respiratory disorders (chiefly emphysema or hypertension) without evidence of gastrointestinal disease.

Finally, to determine the effect of diarrhea *per se* on the fraction of I^{131} excreted in the stool, magnesium sulfate in suitable quantities was administered to a group of subjects without disease of the gastrointestinal tract who had previously received I^{131}-albumin or inorganic iodide^{131}. The daily excretion of radioactivity in urine and stool was assayed by the methods already outlined, both before and during the period of induced diarrhea. In each of these subjects thyroidal concentration of I^{131} was blocked by the administration of Lugol's solution.

RESULTS

The results of the survey of hospital records for the frequency of hypoproteinemia and hypoalbuminemia in patients diagnosed as having regional enteritis or ulcerative colitis reveal a frequent occurrence of disturbances in protein metabolism. (Fig. 1.) The average total protein concentration in the serums of ninety-three patients with ulcerative colitis was 6.63 gm. per cent, with an average albumin value of 3.85 gm. per cent. Thirty-three per cent of the subjects had a total protein concentration below 6 gm. per cent, and thirty-two per cent had albumin values below 3.5 gm. per cent. In twenty-three patients with regional enteritis the average total serum protein concentration was 6.1 gm. per cent, and the average albumin value 3.64 gm. per cent. Forty-eight per cent of the patients had serum total protein concentrations below 6 gm. per cent and thirty-nine per cent had less than 3.5 gm. per cent serum albumin.

The data obtained in the I^{131}-albumin studies are summarized in Tables I and II, and Figure 2. In the last line of Table I are reproduced data on albumin turnover in sixteen normal subjects which have been reported on previously [*28*]. The serum albumin concentration was uniformly subnormal in the patients, ranging from 1.5 to 3.7 gm. per cent with an average of 2.5 gm. per cent, as compared with the average of 3.9 gm. per cent in the control group. Plasma volume, expressed as milliliters per kilogram total body weight, was greater for the patients, in all but one instance, than the average of the control series, 40.5 ml./kg. The average plasma volume for the group of patients was 52.8 ml./kg. The average total circulating albumin in the patients was 1.32 gm./kg., compared with the control average of 1.48 gm./kg. Total exchangeable albumin averaged 3.52 gm./kg. for the patients as compared with 4.23 gm./kg. in the controls. There was some overlap between the two groups, the values for some patients falling within the normal range. In the middle graph of each chart can be found the ratio of circulating albumin to total exchangeable albumin. In the normal, this figure is approximately 0.40, while in edematous patients it may fall as low as 0.25. In most of the present patients the ratio was close to normal, ranging from 0.35 to 0.40.

The average half-time for the degradation of iodinated albumin was 14.4 days in the control group. It was much shorter in the patients reported on here. Expressed otherwise, the control subjects degraded an average of 4.8 per cent of body albumin per day, whereas the patients degraded from 6.2 to 11.5 per cent per day, with an average of 8.6 per cent per day.

TABLE II
FECAL I^{131} EXCRETION IN PATIENTS WITH INTESTINAL DISEASES COMPARED WITH NORMAL SUBJECTS (I^{131}-ALBUMIN ADMINISTERED INTRAVENOUSLY)

Chart No.	Diagnosis	Per cent of Body I^{131}-Albumin in Daily Stool	Per cent of Total Daily I^{131} Excretion in Stool
014526	Ulcerative colitis	1.3	33.0
015080	Ulcerative colitis	0.6	18.0
016083	Ulcerative colitis	0.5	17.0
016997	Regional enteritis	0.1	2.0
014544	Regional enteritis	1.6	22.0
014835	Regional enteritis	0.1	2.6
016829	Inactive regional enteritis	0.06	1.0
Control subjects (average of nine studies)		0.03	0.6

TABLE III
AVERAGE STOOL I^{131} CONTENT IN THREE CONTROL SUBJECTS FOLLOWING INTRAVENOUS ADMINISTRATION OF IODIDE^{131} OR I^{131}-ALBUMIN

Data	Stool Weight (gm.)	Per cent Daily I^{131} Excretion in Stool
Iodide^{131}		
Control days	116	0.17
Induced diarrhea ($MgSO_4$)	374	1.10
I^{131}-Albumin		
Control days	103	0.48
Induced diarrhea ($MgSO_4$)	265	1.45

Assuming the patients to be in a steady state, the quantity of albumin synthesized and degraded varied from 0.21 gm./kg./day (in the patient with inactive disease) to a high of 0.41 gm./kg./day, with an average for the group of 0.31 gm./kg./day. Control subjects synthesize and degrade albumin at an average rate of 0.2 gm./kg./day. Thus it is apparent that none of the patients showed evidence of impairment of the ability to produce albumin.

The route of excretion of I^{131} derived from the administered labeled albumin is separately presented in Table II. It may be seen that a much greater than normal percentage of the radioactivity is excreted in the feces of some of the patients. In the samples of stool from the patients with ulcerative colitis which were studied the per cent of radioactivity which was nondialyzable and precipitable with trichloracetic acid averaged 50 per cent, presumptive evidence that iodinated albumin rather than breakdown products was present in the stool.

The results of the study of I^{131} excretion in drug-induced diarrhea are presented in Table III. When diarrhea occurred, as evidenced by an increase in weight of the stool, the fraction of daily I^{131} output in the stool increased. The change was not great, however, and the highest observed fraction of daily excretion accounted for by the stool did not approach the figures encountered in some of the patients with enteritis or colitis. Furthermore, none of the fecal radioactivity could be shown to be protein bound in the subjects with magnesium sulfate-induced diarrhea.

After the intravenous administration of I^{131}-labeled PVP to human subjects, radioactivity in the plasma declined rapidly at first, then more slowly, as had been observed by Ravin, Seligman and Fine [*26*]; graphical analysis of the data revealed a complex curve with no determinable exponential components. The rate of excretion of radioactivity in the urine also was found not to be amenable to analysis into exponential functions. Such a result is not surprising, since PVP preparations are not homogeneous in terms of molecular weight, but rather are composed of a wide range of molecular species, each with its own rate of diffusion and urinary excretion. For these reasons, and because there was no significant difference between normal and abnormal subjects that could be observed in the curves of blood and urine radioactivity, these data will not be presented in detail. The reported stool radioactivity is the cumulative output over a four-day period. The fraction of the dose excreted by this route by patients with regional enteritis or ulcerative colitis was significantly different from that excreted by normal subjects. These results are presented in Table IV, along with some of the more pertinent clinical data of each subject. Although many of the patients studied after the administration of PVP were the same as those tested with labeled albumin, the procedures were necessarily carried out at different times, and for that reason the plasma protein values are not always identical. A survey of these results shows that patients with enteritis or colitis excrete appreciably more of the radioactive polymer in the feces than do normal subjects. A trend toward higher fecal excretion of PVP in the patients with more severe disturbances of protein metabolism is suggested, but the

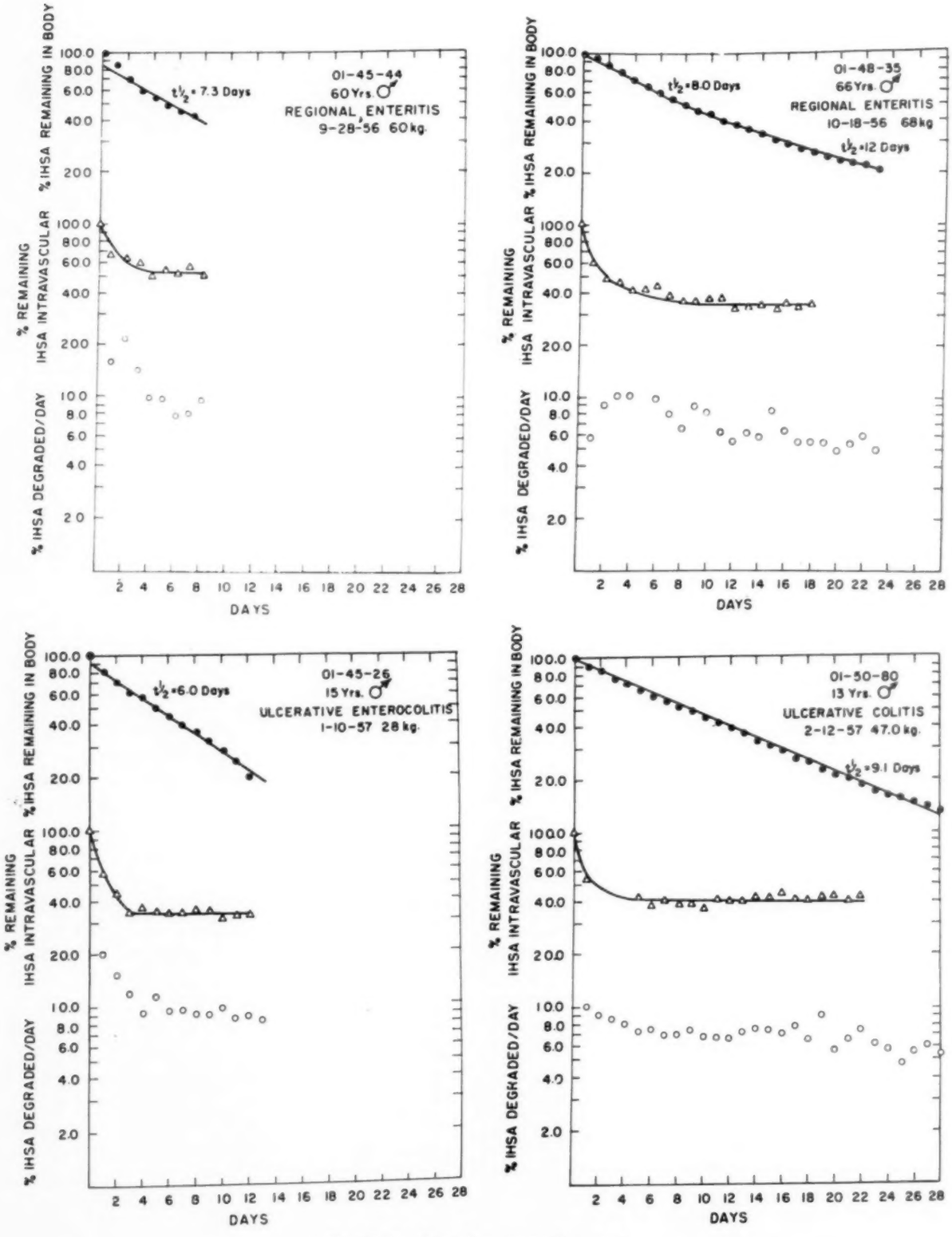


FIG. 2. See legend on opposite page.

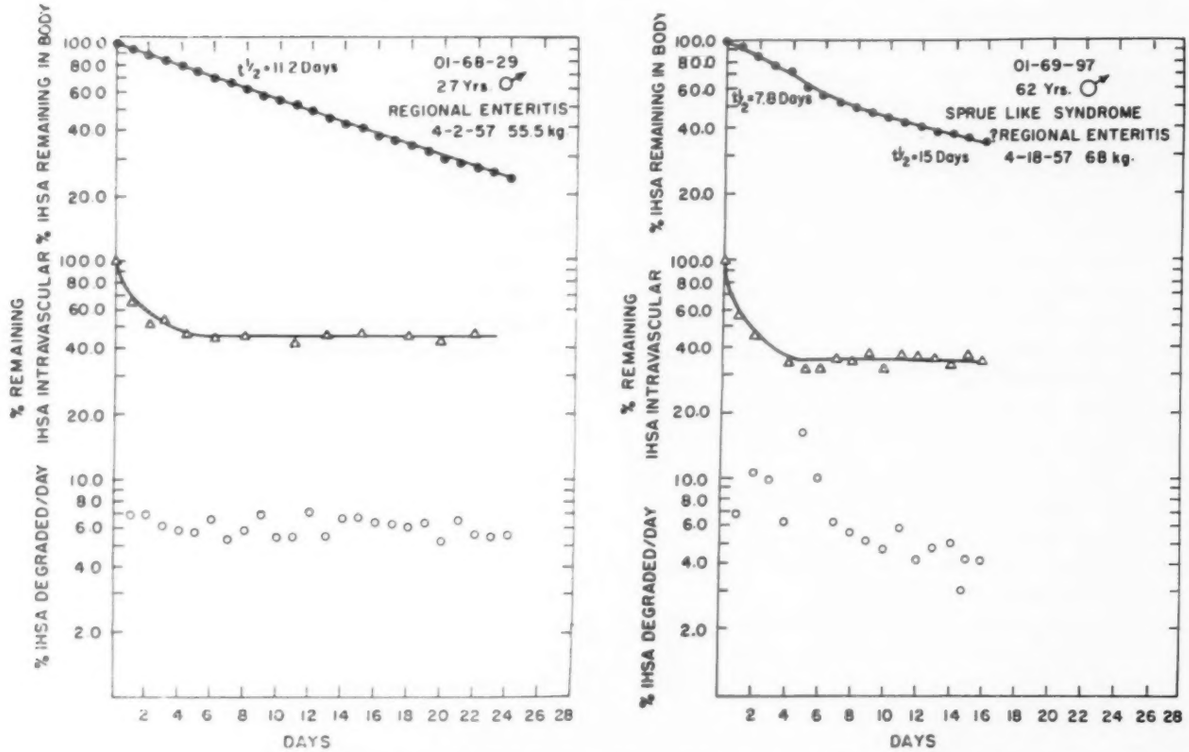


FIG. 2. In the upper portion of each chart is plotted the logarithm of the per cent of the I^{131}-albumin administered remaining in the body as a function of time. In the middle portion of each chart is plotted the time course of distribution of I^{131}-albumin between intra- and extravascular spaces. In the lower portion of each chart is plotted the degradation rate of I^{131}-albumin for each day the patient was studied.

number of patients is too small to permit statistical analysis.

COMMENTS

Data previously reported in the literature [*1–10*], and the values of serum protein concentrations observed in this study, serve to emphasize the frequency with which hypoproteinemia is encountered in patients with active regional enteritis or ulcerative colitis. While no correlation of the degree of reduction of serum protein levels with the severity of the disease process was

TABLE IV

FECAL EXCRETION OF INTRAVENOUS I^{131}-PVP

(PER CENT OF ADMINISTERED RADIOACTIVITY IN FOUR-DAY STOOL)

No. of Patient	Disease	Age (yr.) and Sex	Clinical Status of Disease	Serum Total Protein (gm. %)	Serum Albumin (gm. %)	PVP Excreted (%)
01-48-35	Regional enteritis	68, M	Active	3.7	1.5	7.4
01-45-44	Regional enteritis	63, M	Active	4.5	2.1	5.0
01-94-51	Regional enteritis	44, F	Inactive	6.5	3.5	0.4
01-75-89	Ulcerative colitis	14, M	Active	5.7	3.2	2.6
01-75-47	Regional enteritis	16, M	Active	6.0	2.8	2.8
01-86-30	Ulcerative colitis	52, F	Active	5.7	2.7	2.3
00-08-47	Ulcerative colitis	10, M	Active	6.8	3.8	5.8
01-56-96	Ulcerative colitis	45, F	Active	6.6	3.3	2.5
Normal subjects (9)	...	...	...	...	...	0.16 to 0.63

attempted in the present study, others [*8,11*] have indicated a belief in such a relationship. It seems likely that measurement of the serum protein concentration will prove to be a helpful procedure in estimating the extent and severity of known disease. The results of the present study provide a theoretic basis for, and add support to, the empiric clinical concept that hypoproteinemia is a consequence of the intestinal disease itself, and not of some secondary complication. Further, they support the idea that hypoproteinemia indicates active and extensive disease. Of interest in this regard is that a patient (No. 016829) with evidence of disease on roentgenographic examination of the intestinal tract had a normal albumin turnover when studied. The albumin turnover studies correlated with the present clinical status while the roentgenographic findings showed evidence of the previous anatomic disturbances.

The mechanism of the hypoproteinemia seems reasonably clearly delineated from these results. At least in the group of patients studied intensively, hepatic functional impairment was not present. In particular, the estimated rate of production of serum albumin was not significantly reduced, a finding which is incompatible with the idea that hepatic disease, in the usual sense, could be the cause of the deficiency of circulating albumin. The same can be said for the belief that malabsorption is to blame, as in that case one would expect a decreased rate of albumin synthesis. No one of the patients studied with radioactive albumin or PVP presented the usual clinical picture of severe malabsorption, with gross steatorrhea and great loss of weight. In view of the rather definitive evidence of an abnormally rapid removal of albumin from the circulating plasma, and the decreased body albumin pool, occurring in the absence of any recognizable external loss of the protein (neglecting for the moment the patient in whom a small amount of protein-bound radioactivity could be demonstrated in the feces), it becomes necessary to conclude that albumin is being removed or catabolized internally at an increased rate.

The exact site of physiologic albumin degradation is as yet unknown, although the available evidence points to the liver and, possibly secondarily, to the kidney. There are no data to implicate the gastrointestinal tract in normal albumin catabolism; indeed, the animal experiments of Gitlin, Klineberg and Hughes [*29*] suggest otherwise. The small amount of I^{131}-PVP entering the feces in normal subjects also suggests that transfer of plasma proteins into the gastrointestinal tract is not an important channel for normal catabolism.

It is appropriate at this point to consider the relationship of loss of protein into the gastrointestinal tract to internal degradation. Absorption from the gut of intact protein molecules is a possibility, and appears to have been demonstrated in certain special cases (see Nasset [*19*] for a review of this aspect), but it seems unlikely that the bulk of any plasma protein exuded into the diseased bowel could be reabsorbed; it would probably be excreted in the feces in intact or partially degraded from, or digested by enzymatic action and its split products reabsorbed by the patient. The proportion of exuded protein undergoing each of these fates is undoubtedly determined largely by the location of the diseased segment in which the loss occurs. Since I^{131}-labeled proteins can be used satisfactorily to estimate protein absorption [*30,31*], it is apparent that I^{131}-albumin entering the proximal gut from the plasma would be virtually completely digested and reabsorbed. This possibility is illustrated in the study by Citrin, Sterling and Halsted [*32*], which showed that the site of protein loss was the stomach. At the opposite extreme, our own experience shows that in ulcerative colitis some of the tracer is lost into the stools while still in protein-bound form. When the site of loss is intermediate, as in regional enteritis, little if any protein-bound radioactivity can be demonstrated in the feces. This does not necessarily imply effective digestion by the patient, however, as it may have been the bacteria of the colon that destroyed the protein. Since inorganic iodide can be absorbed from the colon [*33*], bacterial or host digestion of I^{131}-labeled proteins would not be differentiated by our procedures. Nor do these technics differentiate between intraenteric catabolism and catabolism occurring elsewhere in the body of the patient. In either case, the tracer I^{131} is freed as inorganic iodide, reabsorbed if it is freed in the intestine, and excreted in the urine. As a matter of fact, the fate of the albumin molecule is of little importance in this connection, as long as it leaves the plasma and is not returned thereto intact. The quantities of protein lost are small in comparison with the protein content of a normal diet. As long as the dietary intake is adequate, the question of external loss versus

intraenteric degradation of albumin is of only minor importance, and has no bearing on the dynamics of serum albumin metabolism.

The impracticality of intubating patients with the objective of recovering I^{131}-albumin from the lower intestines, and the impossibility of recovering it in the feces, led to the studies with I^{131}-labeled PVP. The tendency of the patients with enteritis or colitis to excrete intravenously administered PVP into stools can be taken as further evidence to support the view that plasma proteins may be lost into the gastrointestinal tract in these subjects.

PVP differs from plasma proteins in regard to molecular shape in solution, lack of surface charge, and in being non-metabolizable. It is similar in being soluble in aqueous and not in lipid media, and in being a macromolecule. The demonstration of a pathway whereby the PVP molecule can pass from the blood to the lumen of the gut makes it seem reasonable that a similar route is available to proteins. It is unfortunate that the molecular inhomogeneity of the PVP preparations commercially available makes a quantitative estimation of the diffusion capacity of this blood-to-gut transfer pathway impossible. The procedure has merit, however, as a qualitative test for abnormal permeability of the gastrointestinal tract, and might be of some use in estimating the degree of protein loss versus malabsorption in a variety of intestinal disorders. The simplicity of the procedure, and the low levels of radioactivity required make it particularly attractive. Finally, it appears that this test may be of use in incriminating gastrointestinal lesions as the site of protein loss in patients presenting hypoproteinemia of otherwise obscure etiology [*34*]. One patient (H. A., No. 01-48-35), is of particular interest in this regard, and is therefore presented in detail subsequently. This subject had had so few symptoms related to enteritis that the disease had been considered to be in remission, until edema developed and caused him once again to seek medical aid. The investigations carried out with labeled albumin and PVP made it clear that his difficulty was due to abnormal loss of protein, and that in all likelihood the intestinal disorder was the offender.

If I^{131}-albumin degradation is increased in patients with ulcerative colitis and regional enteritis as a result of protein loss into the bowel with digestion and/or excretion, what implications does this have for the normal catabolism of serum albumin or other serum proteins? In experiments designed to test the ability of non-essential amino acids to promote growth and maintain nitrogen balance it was found by Elman [*35*] and Geiger [*36*] that all necessary amino acids must be supplied at the same time. A delay of several hours in supplying an essential amino acid resulted in negative nitrogen balance. In a different type of experiment Nasset, Schwartz and Weiss [*37*] found that the total nitrogen recovered from the gastrointestinal tract of dogs fed a non-protein meal increased from duodenum to lower ileum, indicating an accumulation of digestive enzymes and other proteins. Further, when distinctive proteins were fed, the amino acid mixtures recovered from the lower small intestine were similar, possibly pointing to a homeostatic mechanism designed to provide all necessary amino acids at the same time, should protein synthesis by the liver be rapid rather than gradual. If the average fecal nitrogen is 1.5 gm., and is largely from endogenous sources, then 9 gm. of protein are lost via the gastrointestinal tract daily. In describing even the most adamant vegetarian as a cannibal digesting his own digestive enzymes, proteins and desquamating intestinal epithelial cells, Nasset [*19*] estimated that 50 to 100 gm. of endogenous proteins are transferred into the gut each day. Approximately 85 per cent of this amount is reabsorbed either as protein or in the form of breakdown products. The average daily albumin breakdown is 14 gm. [*24,38*]. How much, if any, is "cannibalized" is as yet unknown. The very local fecal output of I^{131}-PVP in normal subjects suggests, however, that the process mentioned is ordinarily not important.

SUMMARY

1. Patients with advanced, active regional enteritis or ulcerative colitis were found to have subnormal serum albumin concentrations, increased plasma volumes, subnormal total body albumin stores, and an increased rate of degradation or loss of I^{131}-labeled albumin.

2. No evidence is offered for or against an absorptive defect in the small intestines of these patients, but it was established that impaired albumin synthesis could not be indicted as the basis for the subnormal body albumin levels, since the rate of albumin synthesis in these patients was found to be greater than that observed in normal subjects. The increased rate of

albumin synthesis, however, did not keep pace with the increased rate of albumin loss or degradation, hence such patients have a subnormal concentration of body stores of albumin.

3. Following intravenous administration of I^{131}-albumin, the stool concentration of free or protein-bound I^{131} was found to be high in the patients with active regional enteritis or ulcerative colitis. In addition, these patients excreted a much larger fraction of intravenously administered I^{131}-labeled PVP in the stools than did normal subjects. These findings suggest that the increased albumin degradation and low body albumin stores in regional enteritis and ulcerative colitis is due to loss of protein into the intestinal tract, with subsequent digestion and/or excretion.

Acknowledgment: We are indebted to Dr. B. Marr Lanman of Schenley Laboratories, Inc. who provided the sample of PVP K-30.

APPENDIX

Case Report

H. A., (No. 014835), is a manufacturing executive born in 1890. He was well until 1947, when abdominal pains lasting over a period of six months led him to undergo exploratory laparotomy at another hospital. The diagnosis of regional enteritis was made on the basis of gross pathology. Though no surgical therapy was then attempted, his symptoms were alleviated postoperatively, and he considered himself well. He consumed a normal diet, had one formed stool per day, and suffered no pain. In 1956 he again sought medical aid because of four months of increasing dependent edema, unaccompanied by other symptoms. He was admitted to another hospital, where hypoproteinemia was discovered. Partial control of his edema was achieved with diuretic drugs. He was admitted to the Clinical Center, National Institutes of Health, later the same year. Physical examination revealed an elderly man in no distress. The vital signs were normal except for a blood pressure of 160/70 mm. Hg. The liver was just palpable; the only other physical finding of significance was massive edema of the ankles and lower extremities extending upward to the iliac crests bilaterally. Laboratory data were as follows: hemoglobin 12 to 13.5 gm. per cent on repeated determinations; white blood cells 5,000 to 6,000 per cu. mm. with normal differential counts; mild microscopic hematuria, and mild albuminuria ranging from 1.7 to 2.6 gm. of protein excreted per day; stools negative for occult blood, ova and parasites. Blood chemistries were as follows: serum electrophoresis; albumin 1.54 gm. per cent, $alpha_1$ globulin 0.57 gm. per cent, $alpha_2$ 0.90 gm. per cent, beta globulin 1.00 gm. per cent; blood urea nitrogen 33 to 41 mg. per cent, creatinine 1.7 mg. per cent; electrolytes were within normal limits, except for potassium which ranged from 5.6 to 6.2 mEq./L.; total cholesterol was 157 mg. per cent. Retention of bromsulphalein was 4 per cent at 45 minutes. Roentgenographic examination of the gastrointestinal tract revealed extensive changes typical of regional enteritis extending from mid-jejunum to lower ileum. The terminal ileum, well outlined in a barium enema, showed only mild changes. No fistulous tracts were observed. Results of a test of absorptive capacity with I^{131}-triolein were normal (less than 5 per cent of the dose in the stools). Studies with I^{131}-albumin and I^{131}-PVP have been described. He was treated initially with sodium restriction and diuretic drugs, with almost complete clearing of his edema. Over the subsequent two years, however, his condition has gradually become worse, and response to diuretic therapy decreased. This has been associated with progressive renal functional impairment. Human serum albumin in large amounts has been administered intravenously; the results of this therapy have been gratifying, but not enduring. No symptoms directly referable to the regional enteritis have developed, and the status of the disease by roentgenograms has not changed significantly.

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Amyloidosis in Regional Enteritis*

A Report of Five Cases

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It has not been generally appreciated that in a significant number of patients with regional enteritis amyloidosis can develop in the course of their illness. The first such case was reported in detail in 1949 [*1*], and there have been only five cases noted in the literature up to the present time [*1–4*]. Among thirty-nine patients with regional enteritis who died, at the Mayo Clinic, two instances of amyloidosis were found at autopsy [*4*].

During the past twenty years autopsies were performed on seventeen of the twenty-three patients who died at The Mount Sinai Hospital as a result of regional enteritis. A review of these findings has disclosed that in addition to the patient reported on by Cohen and Fishman [*1*], amyloidosis was found in four others, a surprisingly high incidence (29.4 per cent). In three of the instances noted here, amyloidosis was a major factor among the causes of death. Amyloidosis therefore appears to be a more frequent fatal complication of the disease than is generally appreciated, and its appearance serves as an indication for surgical removal of the diseased bowel.

Of the five patients in whom amyloidosis was found at autopsy, three were men and two were women. They ranged in age from thirty to seventy years. In Table I several factors possibly predisposing to amyloid deposition (chronic suppuration, prolonged or extensive enteritis, and the administration of steroids) are summarized for each patient. Symptoms attributable to the enteritis preceded the postmortem demon-

Table I

FACTORS POSSIBLY PREDISPOSING TO AMYLOID DEPOSITION

Case No.	Duration of Enteritis (yr.)	Extent of Enteritis	Chronic Suppuration	ACTH or Steroid Therapy
I	14	20 in. terminal ileum and multiple proximal skip areas following surgery	None	10-day course of ACTH given two weeks before death
II	8	9 cm. terminal ileum; colon to sigmoid flexure (granulomatous type), a short segment of jejunum	Anal ulcer and perirectal abscess	None
III	10	9 cm. of terminal ileum and a 60 cm. segment of jejunum	None	None
IV	4	45 cm. of terminal ileum	None	None
V	10	25 cm. of terminal ileum	Fecal fistulas; chronic retroperitoneal abscess; osteomyelitis of the fourth lumbar vertebra	None

* From the Division of Gastroenterology, the Department of Medicine, and the Department of Pathology, The Mount Sinai Hospital, New York, New York. Aided by a grant from the Institute of Arthritis and Metabolic Diseases of the U. S. Public Health Service.

TABLE II

CLINICAL MANIFESTATIONS OF AMYLOIDOSIS COMPLICATING REGIONAL ENTERITIS

Case No.	Diagnosis Suspected	Hepatomegaly	Splenomegaly	Renal Status	Congo Red Retention	Gingival Biopsy	Liver Biopsy
I	Yes	None	None	Nephrotic syndrome and progressive uremia	38% $\bar{p}$ 1 hr.	Normal	...
II	Yes	Present	Present	Nephrotic syndrome and progressive uremia	...	Normal	...
III	Yes	Present	Present	Nephrotic syndrome and progressive uremia	Equivocal*	Normal	Normal (3 mo. before death)
IV	No	None	None	Normal	...	...	...
V	No	Present	Present	Normal	...	...	...

* Seventy-five per cent retention. Test considered to be equivocal because of heavy output of dye in the urine.

stration of amyloidosis by four to fourteen years; however, neither the dates of onset of the enteritis nor of the amyloidosis could, of course, be determined precisely. In three patients (Cases III, IV and V) the enteritis was only moderate in extent, and in one (Case II) there was involvement of the colon as far as the sigmoid flexure, but only two short segments of enteritis involved the small bowel. In this latter instance the involved colon was resected four years prior to death, and three years prior to the onset of the progressive clinical picture of amyloidosis. Chronic external fistulas or suppuration had been present in only one patient (Case V). In this instance a retroperitoneal abscess was present and had caused osteomyelitis of an adjacent vertebral body. One other patient (Case II) had had repeated fissures-in-ano and a perirectal abscess as the initial symptom of her enteritis: these lasted one year and preceded the onset of clinical amyloidosis by six years without recurrence in the interval. In Case I, ACTH or adrenal steroids had been administered, but for only a ten-day period during the terminal stages of his illness.

In Table II the clinical manifestations of amyloidosis complicating regional enteritis are summarized. The liver and spleen were considered to be enlarged in three cases. In three patients the typical manifestations of the nephrotic syndrome were present. In one of these patients (Case III), there was progressive renal failure, and death followed the appearance of peritonitis which complicated the nephrotic syndrome and ascites. In another (Case II), there was profound uremia and death in convulsions. The third (Case I) died with progressive uremia and inanition, complicated by adrenal hemorrhage and necrosis. In three cases the diagnosis of amyloidosis was suspected on clinical grounds; in two because of the presence of hepatosplenomegaly and the nephrotic syndrome and in one instance because of marked proteinuria, edema and evidence of adrenal insufficiency. In all cases the blood pressure remained normal. In no instance was the diagnosis confirmed prior to autopsy. In three cases a gingival biopsy was free of amyloid, as was the biopsy of the liver in one patient. In two patients a Congo red test failed to give diagnostic results.

CASE REPORTS

CASE I. S. B., a twenty-four year-old white man, was first admitted to The Mount Sinai Hospital in April 1938 because of diarrhea and crampy lower abdominal pain of one year's duration and a weight loss of twenty pounds. There was a tender mass in the right lower quadrant of the abdomen which at operation was found to be a segment of granulomatous ileitis involving the terminal eighteen to twenty inches of ileum. An ileotransverse colostomy with transection of the ileum six inches proximal to the diseased segment was performed. The patient subsequently gained thirty pounds and remained asymptomatic for two years when there was recurrence of diarrhea and crampy abdominal pain. In 1942 barium meal roentgenographic examination of the small intestine showed extensive recurrence of the disease in the new terminal ileum, with proximal distention of small bowel. In October 1943 an emergency Witzel tube ileostomy was performed because of acute obstruction

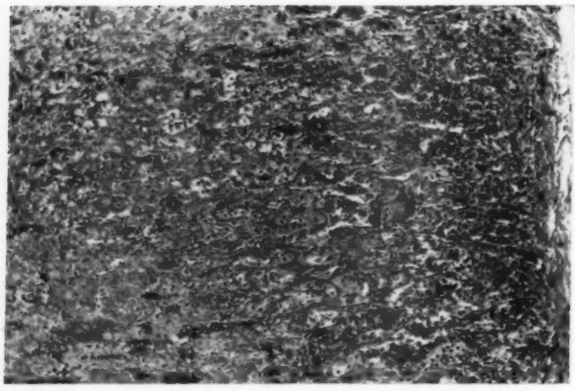


FIG. 1. Case I. Amyloid deposition in the adrenal cortex. Death resulted from adrenal hemorrhage and necrosis. Hematoxylin and eosin × 63.

of the small bowel, and one month later a new ileotransverse colostomy was constructed and two segments (measuring 3 inches and 18 inches) of stenotic granulomatous enteritis proximal to the old ileocolostomy were resected. The original excluded terminal ileum was found to be atrophic, and without evidence of disease. At this time proteinuria (1 plus) was noted for the first time. In May 1944 an elective resection of the excluded ileum and right colon was performed. The surgical specimen showed atrophy and linear scarring of the terminal ileum, with no evidence of fistulas, abscess or active disease. Two years later there was a recurrence of symptoms and in September, 1949 he was admitted to the hospital for the fourth time because of anemia, weakness and fatiguability. The anemia was macrocytic and responded well to parenteral administration of vitamin B_{12}. At that time the serum albumin was 3.2 gm. per cent, the serum globulin was 2.8 gm. per cent. The urine contained a trace of protein. In January 1951 the fifth admission to The Mount Sinai hospital took place because of increasing weight loss, diarrhea and crampy abdominal pain. No abdominal organs were palpable. For the first time there was 4 plus proteinuria. The urine was normal on microscopic examination. The blood urea nitrogen was 10 mg. per cent. The serum albumin was 2.3 gm. per cent; the serum globulin 3.4 gm. per cent. Small bowel barium roentgenographic series showed extensive recurrent inflammatory disease in the remaining ileum. In June 1951 he was admitted to the hospital for the last time. He complained of pain in the right flank of two weeks' duration, and a tender fluctuant mass was found in this region. The blood pressure was 90/60 mm. Hg. The patient appeared emaciated. No organs were palpable. The large abscess in the right abdomen was drained, and all the remaining small bowel except for the proximal 18 inches of jejunum was resected and a jejunotransverse colostomy was constructed. The surgical specimen consisted of a 75 cm. segment of small intestine showing diffuse acute and chronic granulomatous enteritis. No chronic abscesses or fistulas were described. Following surgery severe dependent edema developed. The urine was found to contain up to 15 gm. of protein per day, as well as many red and white blood cells and hyaline casts. Results of a test for Bence Jones protein were negative. The serum albumin fell to 1.3 gm. per cent, and did not improve significantly despite the intravenous administration of large volumes of salt-poor human albumin. The patient became progressively uremic. Amyloidosis was suspected clinically, but a biopsy of the liver and re-examination of the resected bowel showed no amyloid deposits. A Congo red test showed 38 per cent retention after one hour. There was a normal eosinopenic response to ACTH, and a course of this drug was given for ten days; this was stopped three days before his death. He became increasingly debilitated and died during a bout of diarrhea fourteen weeks after the last intestinal resection.

Autopsy findings were as follows: the small intestine measured 70 cm. in length and was slightly dilated. It was anastomosed to the mid-transverse colon. The large intestine otherwise appeared to be normal. Multiple, thick, fibrous adhesive bands traversed the peritoneal cavity. No fistulas, sinuses or chronic abscesses were found. Both adrenals exhibited severe and diffuse amyloid deposition (Fig. 1) as well as necrosis, hemorrhage and multiple venous thromboses. Amyloid was also present in the arteries and arterioles of the bone marrow, kidneys, urinary bladder, prostate, testes, colon, lung, lymph nodes, liver, spleen, pancreas and sweat glands. The liver weighed 1,620 gm. and contained amyloid only in the walls of blood vessels. The spleen weighed 170 gm. and was diffusely infiltrated by amyloid. Both the liver and spleen were acutely and chronically congested. Extensive amyloidosis of the kidneys was noted, with deposits in the glomeruli and around the basement membranes of the tubules. There was also an acute focal interstitial pancreatitis with evidence of acute inflammation and fat necrosis in nearby tissues. Death was caused by adrenal necrosis and hemorrhage.

CASE II. F. F., a married white woman twenty-four years of age, was admitted to The Mount Sinai Hospital in June 1949 for the first time with complaints of diarrhea, weakness, anorexia, weight loss and intermittent fever of two years' duration. Six years previously she had had rectal pain, and bleeding on defecation, and following excision of an anal ulcer a perirectal abscess developed which drained small amounts of grey material intermittently for one year. Histologic examination of the excised tissue was said to have shown chronic granulomatous inflammation considered by a pathologist to represent tuberculosis. Acid-fast bacilli were seen in several random urine specimens, but these could not be grown by culture or guinea pig inoculation. She had received a course

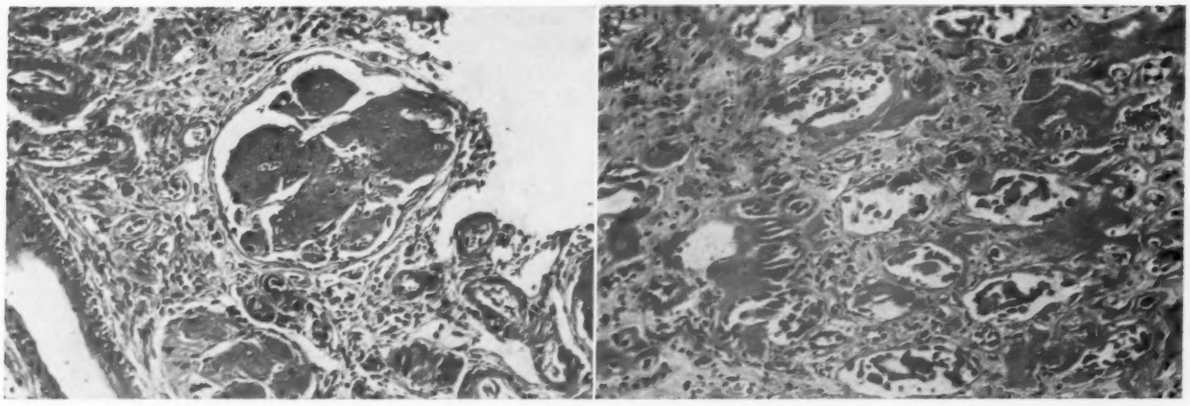


FIG. 2. Case II. Amyloidosis of the kidney. The patient died with renal failure. Hematoxylin and eosin × 120.

of chalmoogra oil, promizole and streptomycin which were discontinued when the bacteriologic studies failed to confirm the diagnosis.

At the time of admission to this hospital she appeared thin and chronically ill. There was clubbing of the fingers and toes. The abdomen was soft and non-tender. The spleen was palpable 2 cm. below the left costal margin. There was an anal fissure and a rectal stricture 3 to 4 cm. above the anus. The blood hemoglobin was 11 gm. per cent. Results of urinalysis were negative. The serum albumin was 2.8 gm. per cent; serum globulin 3.6 gm. per cent. Barium enema roentgenographic examination of the colon showed narrowing and irregularity of the colon from the cecum to the splenic flexure. Barium meal roentgenographic examination of the small bowel showed similar inflammatory changes involving 9 cm. of terminal ileum. Sigmoidoscopy showed the rectal mucosa just below the stricture to be granular.

In August 1949 she was readmitted because of exacerbation of symptoms. The liver and spleen were palpable 2 cm. below the costal margins. There was a trace of protein in the urine. Guinea pig inoculations, smears and cultures of urine and stool for tubercle bacilli were carried out. Despite negative results in all of these studies a course of streptomycin was given, with no improvement. Sigmoidoscopy showed a somewhat friable mucosa at the rectal stricture, but no other abnormalities. In November 1949 an ileostomy was performed 3 inches proximal to the diseased ileum. Following this the patient felt well and gained 15 pounds.

In September 1950 because of malaise, weight loss and the passage of blood from the rectum, a subtotal ileocolectomy removing the bowel previously excluded by ileostomy, as far as the lower sigmoid colon, was performed. The pathologist reported the colon and ileum to show marked thickening and many epithelioid granulomas, the process being most marked in the ileum and in the splenic flexure of the colon. The lower sigmoid and rectosigmoid were free of disease. At that time there was 2 plus proteinuria, the serum albumin was 3.9 gm. per cent, and the blood urea nitrogen was 8 mg. per cent.

An uncomplicated pregnancy was completed in January 1952 with spontaneous delivery by the normal route of a full term, healthy baby.

Subsequently, she was well for a year, but in 1953 noted return of malaise and nocturnal fever. In 1954 anorexia, weakness and weight loss returned. In June 1955 the blood pressure was 106/58 mm. Hg. The liver and spleen were still palpable 2 cm. below the costal margins. The urine contained 2 plus protein, 3 to 5 red blood cells, and 3 to 5 white blood cells per high power field. The blood urea was 50 mg. per cent. The serum albumin was 3.2 gm. per cent; the globulin 2.5 gm. per cent. The blood hemoglobin was 8.2 gm. per cent. Amyloidosis was suspected on clinical grounds, but biopsy specimens of the gingiva and rectum were free of amyloid deposits.

In August 1955 she was found to have 4 plus proteinuria with many white blood cells in casual urine samples. The blood urea nitrogen was 65 mg. per cent. She became progressively weaker, edema and cachexia developed. Uremia increased rapidly; the blood pressure remained within normal limits. In September 1955 she died with severe uremia, convulsions and gastrointestinal bleeding.

Autopsy findings were as follows: approximately 4 feet from the ligament of Treitz the small intestine was dilated for a distance of 15 cm. Just distal to this a short segment of bowel was thickened (as was its mesentery) and somewhat narrowed. The mucosa here was atrophic, scarred and deeply ulcerated along the mesenteric border. Histologically, this segment exhibited acute and chronic non-specific granulomatous enteritis. A large amount of blood within the intestinal tract had its origin in the diseased segment of bowel. The colon had been subtotally resected and the remaining sigmoid colon and rectum appeared normal, except for atrophy of the mucosa. No abscesses or fistulas were found. Amyloid deposits were noted in the central portion of the adrenal cortex, as well as in the blood vessels of the pancreas, spleen,

bone marrow and the liver. The latter was not otherwise involved and weighed 1,500 gm. The spleen weighed 300 gm. and contained amyloid deposits in the Malpighian corpuscles, arterioles and sinusoidal reticulum. The kidneys were severely involved by amyloid deposits in the glomeruli, the arterioles and the stroma surrounding the collecting tubules. (Fig. 2.) A small collection of mercury was found in a group of alveoli in the right lung, surrounded by a granulomatous reaction. Death was caused by renal failure secondary to amyloidosis and to intestinal bleeding.

CASE III.* H. E., a twenty-two year old woman, was first admitted to The Mount Sinai Hospital in February 1936 because of lower abdominal cramps, blood-streaked stool and intermittent diarrhea for one month. Results of urinalysis were normal. Sigmoidoscopy showed mild inflammation of the rectum and rectosigmoid. Barium enema roentgenographic examination failed to show any evidence of ulcerative colitis. Blood urea nitrogen, serum proteins and cholesterol were normal. Following a course of carbarsone and emetine she was treated symptomatically, but continued to have recurrent bouts of diarrhea. In 1937 she had an episode of erythema nodosum. In 1938, because of pain in the right lower quadrant, nausea, vomiting and fever, an appendectomy was performed. The terminal ileum was found to be markedly thickened and indurated, as was its mesentery, and was considered by the surgeon to represent granulomatous regional enteritis. The pathologic specimen showed acute and chronic appendicitis. Intermittent diarrhea, abdominal cramps, fever and anemia persisted. In 1941 barium meal and barium enema roentgenographic examinations revealed narrowing, rigidity and irregularity of the terminal ileum, but no other abnormality. In June 1945 she was hospitalized because of edema of the ankles and periorbital areas which progressed to generalized anasarca. The blood pressure was 125/88 mm. Hg. There was a hypochromic anemia and severe proteinuria. The serum albumin was 1.8 gm. per cent, and the serum globulin 2.3 gm. per cent; the serum cholesterol was 420 mg. per cent, and total serum lipids were 906 mg. per cent. The blood urea nitrogen was normal. A Congo red test showed 75 per cent disappearance of the dye after one hour, but there was a heavy loss in urine which rendered the test equivocal. The basal metabolic rate was minus 21 per cent. Barium meal roentgenographic examination demonstrated a short stenotic area in the lower jejunum. A biopsy specimen of the liver failed to show any amyloid deposition. She improved temporarily on a program of high protein diet and diuretics, but in December 1946 hypogastric pain, vomiting, nausea and fever suddenly developed. The abdominal wall was rigid, and there was severe diffuse abdominal tenderness. Chemical examination of the blood showed no change from the previous admission, except for an increase in the blood urea nitrogen to 72 mg. per cent. Despite Miller-Abbot intubation, antibiotics and blood transfusions she became increasingly uremic and, following the appearance of convulsive seizures, died.

Autopsy findings were as follows: A 60 cm. segment of jejunum showed alternating areas of stenosis and dilatation, neither of which were extreme. The mucosa was polypoid, scarred and irregularly ulcerated. The terminal 9 cm. of ileum were extremely thick-walled and stenotic, and its mucosa was atrophic and scarred. Some scattered mucosal ulcers and scars were noted just proximal to both diseased segments. The remainder of the bowel was normal. Fistulas were absent, but six tiny sinuses extended along the mesenteric border of the involved jejunum. There was an acute fibrinopurulent pelvic peritonitis.

The liver weighed 1,675 gm. and was free of amyloid, except for the hepatic arteries and arterioles. The spleen was small, but very firm and was the site of widespread amyloidosis of both nodular and diffuse distribution. The normal Malpighian follicles were absent. Heavy amyloid deposition was noted in the adrenal cortex and moderate amounts in the periadrenal vessels. Amyloid was also demonstrated in the heart, endometrium, skin, thyroid, pancreas, and in the walls of blood vessels in the pancreas, ovary, thyroid, kidney and gastrointestinal tract. The kidneys were markedly affected, with partial or total replacement of almost every glomerulus by amyloid; a lesser amount was deposited around the basement membrane of the tubules. Multiple dilated tubules were filled with eosinophilic casts. The renal cortex was diffusely scarred and showed a heavy plasmocytic and lymphocytic infiltration. Death was considered to be caused by uremia, complicated by acute pelvic peritonitis.

CASE IV. N. L., a seventy year-old white man, was first admitted to The Mount Sinai Hospital in September 1939 because of four months of cramping periumbilical pain. He had lost 30 pounds in the year preceding admission. The only previous gastrointestinal symptoms consisted of a one-month episode of diarrhea four years prior to admission. On physical examination the abdomen was soft and not distended. The hemoglobin and white blood cell count were normal. Guaiac tests of the stool for blood were negative. Barium meal roentgenographic examination of the small bowel showed the terminal ileum to be rigid and irritable. While under observation in the hospital, fever and a right lower abdominal mass developed, and in December, 1939 laparotomy revealed the terminal ileum to be involved by typical regional enteritis for 45 cm. proximal to the ileocecal valve. There was a small sealed-off perforation of this segment with an abscess of recent origin adjacent to

* This case has been previously reported [*1*].

the dome of the bladder. This was drained, the diseased ileum was resected to 3 inches proximal to the ileocecal valve, and an ileotransverse colostomy constructed. The surgical specimen consisted of a 40 cm. segment of ileum with a very thick wall. The mucosa was cobblestoned and showed longitudinal scarring. There were a few ulcerations at the line of resection. Following surgery the patient had symptoms and signs of pneumonia of the right lower lobe. He died on the fourth postoperative day.

Autopsy findings were as follows: typical regional enteritis involved the 3 inch terminal ileal remnant. The colon and remaining small bowel were normal. No fistulas or sinus formations were noted. The four day old surgical wound was acutely infected, and acute fibrinopurulent peritonitis was noted. A confluent bronchopneumonia was considered to be the cause of death. Amyloid deposits were found in focal areas of the spleen, which was also moderately congested. (Fig. 3.)

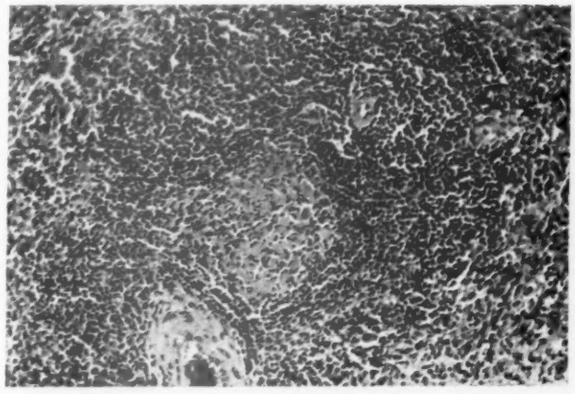


FIG. 3. Case IV. Amyloid deposition in the spleen. There was no other evidence of amyloidosis at autopsy. Hematoxylin and eosin × 120.

CASE V. S. L., a thirty year old white man, was first admitted to The Mount Sinai Hospital in November 1938. Five years previously he had had a perirectal abscess drained by surgical incision. For five years he had noted painless bilateral scrotal enlargement. Seven months before admission an appendiceal abscess was drained at another hospital. This was followed by persistent formation of fecal fistulas which failed to respond to fistulectomy and appendectomy. On admission he was found to have multiple fecal fistulas in the right lower quadrant abdominal scar. The spleen was palpable. There was elephantiasis of the penis and scrotum. At operation, the terminal ileum appeared dilated and dull red, and there were perforations of the cecum and terminal ileum. An attempt to close these was made, but postoperatively a large retroperitoneal abscess developed, requiring drainage. Shortly thereafter the fecal fistulas recurred, and an ileotransverse colostomy with transection of the ileum proximal to the fistula was perforated. He improved and was discharged eighteen weeks after admission, with a small draining sinus in the right lumbar area.

During the following two years he was readmitted on three occasions for plastic surgical procedures to correct the scrotal elephantiasis. In October 1942 a copious foul discharge from the draining sinus appeared, and he was again admitted to the hospital. On physical examination he appeared acutely ill. His temperature was 104°F. The liver and spleen were palpable. The urine showed a trace of protein. There were multiple sinuses of the abdominal wall from which foul material issued. Despite repeated attempts at incision and drainage, chemotherapy and transfusions, his condition progressively deteriorated, and he died in a state of cachexia with high fever, psychosis and terminal pulmonary edema.

Autopsy findings were as follows: advanced chronic regional enteritis of the terminal 25 cm. of ileum was present, as well as a fistula between terminal ileum and cecum; the remaining small and large intestine was spared. A huge retroperitoneal abscess was associated with necrotizing osteomyelitis of the fourth lumbar vertebra. There was cachexia, pulmonary edema and marked lymphedema of the scrotum. Amyloidosis was limited to the liver and spleen, the latter being more heavily involved. Eosinophilic deposits were noted in the kidneys with questionable staining properties of amyloid. The cause of death was considered to be sepsis and cachexia.

COMMENTS

Amyloidosis secondary to inflammatory disease of the intestinal tract has been recorded infrequently. Although chronic ulcerative colitis is often considered to cause amyloidosis, this association has been reported in the literature only six times [*5–9*]. In 1955 Mandelbaum and Bryk [*9*] reviewed 107 autopsies of patients who died of chronic ulcerative colitis at The Mount Sinai Hospital and found only two instances of secondary amyloidosis. Whereas this experience would not justify the assumption often made about the association of amyloidosis and colitis, just the opposite state of affairs seems to exist in regard to the incidence of amyloidosis complicating regional enteritis. Here again the number of reported cases has been small; however, recently Chapin et al. [*4*] noted two instances of amyloidosis in a review of thirty-nine autopsy cases of regional enteritis at the Mayo Clinic. From this observation they suggest "that amyloidosis is not as uncommon a complication of regional enteritis as would be supposed from the scarcity of reported cases." The occurrence of

five cases of amyloidosis in the present series of seventeen autopsy cases of regional enteritis lends strong support to this viewpoint and leads us to suggest that amyloidosis is, in fact, one of the more common fatal complications of regional enteritis. The over-all incidence of amyloidosis in regional enteritis has not been established.

In amyloidosis secondary to ulcerative colitis, chronic peri-intestinal suppuration and the formation of fistulas have been considered by some as the inciting mechanism [*7*]. It is notable that in three of our cases no such gross suppurative process or fistulas were found. In another patient (Case II), the presence of a chronic anal ulcer early in the course was temporally quite unrelated to the onset and progression of the amyloidosis. In only one patient (Case V) could one attribute the amyloidosis to the suppurative or fistulous complications of the enteritis rather than to the local disease process itself. It would seem acceptable to consider the local disease process with its characteristic multiple microscopic submucosal abscesses and tiny intramural sinus tracts adequate explanation for the development of amyloidosis. Whether one wishes to attribute the secondary amyloidosis to this local process, to the chronic granulomatous lesion itself, or perhaps to some primary disturbed immunologic mechanism responsible in parallel fashion for both the enteritis and the amyloidosis, it seems essential to note that amyloidosis in regional enteritis is not dependent upon chronic extra- or peri-intestinal suppuration or fistula formation.

It has not been possible from this small series to reach any conclusions about the relationship between the extent or duration of the enteritis and the development of amyloidosis. In view of the many cases in which extensive enteritis persists for many years without amyloidosis, one must postulate that some other predisposing or precipitating factor is present in those patients with amyloid deposition. From experimental evidence indicating that the administration of ACTH and cortisone may enhance amyloid deposition and delay its reabsorption [*10*], these agents, so often employed in the present day treatment of regional enteritis, become suspect. Our experience fails to support this suspicion. In only one instance reported here was ACTH or cortisone given, and then only during a two-week period on the final hospital admission. Of the many patients with regional enteritis treated here with ACTH or the adrenal steroids, none, to our knowledge, has had amyloidosis.

The distribution of organ involvement by amyloid in this series followed the pattern usually seen in secondary amyloidosis. A notable exception to this was the absence of hepatic amyloidosis (except for arteriolar involvement) in four of our patients. In the fifth patient (Case V) there was typical hepatic involvement but in that instance the amyloidosis might have been attributed to chronic extraintestinal suppuration. In view of the variability of organ involvement seen in amyloidosis of any cause, we would not suggest that this observation in a limited series has any significance. However, an interesting comment in this regard is made by Kleckner [*11*] who, in reviewing the hepatic changes in regional enteritis, states that: " . . . hepatic amyloidosis has not been observed in regional enteritis." This point may be clarified by future observations.

The presence of renal failure in three of our cases is in accord with the reported 70 per cent incidence [*12*] of this complication in patients who died of secondary amyloidosis.

Keith and Daugherty [*13*] have recently described the appearance of the nephrotic syndrome in a patient with regional enteritis. This occurred when there was extensive involvement of the small bowel in the inflammatory process, and resolution of the nephrotic episode did not begin until after removal of a large section of diseased bowel. We suggest that amyloidosis was responsible for the nephrotic episode, and the resolution was secondary to removal of the inciting process.

In view of the failure of any available therapeutic agents to affect favorably the course of amyloidosis (except for amelioration of adrenal insufficiency by the administration of adrenal steroids), it is logical that treatment should be directed at the underlying disease. With this in mind, we submit that when there is clinical evidence that amyloidosis has complicated regional enteritis, indication exists for surgical excision of the involved gut and existing fistulas with adequate drainage of any extraintestinal abscesses, provided the extent of the enteritis and the patient's condition make this feasible. The over-all incidence of amyloidosis in regional enteritis does not warrant prophylactic resection of the diseased bowel.

SUMMARY

1. Amyloidosis was found at autopsy in five of seventeen patients who died as a result of regional enteritis or its complications.

2. In two of the cases presented, death was due to renal failure resulting from renal amyloidosis; in one other, renal and adrenal amyloidosis were significant factors in the fatal outcome.

3. The occurrence of amyloidosis could not be related to the duration or extent of the enteritis, or to the presence of gross suppuration or the formation of fistulas.

4. It is suggested that clinical evidence of amyloidosis appearing in the course of regional enteritis constitutes an indication for resection of the diseased bowel.

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Trypsin, Trypsinogen and Trypsin Inhibitor in Human Pancreatic Juice

Mechanism for Pancreatitis Associated with Hyperparathyroidism

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THE etiology of pancreatitis remains obscure but it is agreed by many that an important factor in this disease is the digestive action of the pancreatic proteolytic enzymes. The enzymes that are likely to be directly concerned with this action are trypsin and chymotrypsin. Each enzyme is normally synthesized in the acinous cell and secreted into the pancreatic duct system in precursor form. Normally, it is not until their entrance into the duodenum that the precursors become activated. Enterokinase, an enzyme secreted by the duodenal mucosa, catalyzes the conversion of trypsinogen to trypsin, but not that of chymotrypsinogen. Many investigators have shown that trypsinogen undergoes autocatalysis, but chymotrypsinogen does not. Neurath [*1*] has presented evidence to indicate that only one peptide bond is split during the activation of trypsinogen, resulting in the liberation of a hexapeptide. Many of the aforementioned experiments have been performed on pancreatic juice or extracts from species other than man. Others experiments have been performed on purified enzyme systems which may not necessarily define relationships in human pancreatic juice.

Nemir and Drabkin [*2*] have shown that when an incubated mixture of blood and activated pancreatic juice is injected into the pancreatic duct of dogs an acute hemorrhagic necrotizing pancreatitis which closely resembles the corresponding disease in man results. Elliott, Williams and Zollinger [*3*] have shown that introduction of an incubated mixture of either bile and activated pancreatic juice or bile and trypsin into the pancreatic duct of the dog will produce a severe acute pancreatitis. Hosie and Ziffren [*4*] have demonstrated that inactivated pancreatic juice contains the enzyme collagenase. They postulate that this enzyme will digest the interstitial tissue of the pancreas and will initiate pancreatitis upon escaping from the duct. They indicate that the product of this action has the ability to transform trypsinogen to trypsin which may produce further destruction.

It becomes apparent that one of the keys to the production of pancreatitis is the transformation of trypsinogen to trypsin and that the newly formed trypsin is to be permitted by its chemical environment within the pancreas to maintain proteolytic activity. It has been demonstrated that trypsin inhibitors are present in a variety of body fluids such as colostrum, blood serum and canine pancreatic juice [*5–7*]. The role and importance of the pancreatic trypsin inhibitor in animals has not been fully evaluated and studies in man are lacking.

The purpose of this study is (1) to investigate factors responsible for the activation of trypsinogen to trypsin in pancreatic juice in human subjects, (2) to determine whether or not human pancreatic juice has trypsin inhibitor, and (3) what the role of the trypsin inhibitor is.

METHODS AND MATERIALS

The method for determining tryptic activity is a modification of that developed by Karmen utilizing the synthetic substrate benzoylargininеparanitroanilide (BAPNA). Trypsin splits this substrate to yield benzoylarginineamide and the yellow dye, paranitroaniline. BAPNA is synthesized by heating an equimolar mixture of paranitroanaline hydrochloride

* From the School of Medicine, University of Southern California, and The Los Angeles County Hospital, Los Angeles, California. This work was supported by Grants A-1992 and 2A-5049 from the National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, and a grant from the San Diego Health Foundation.

TABLE I

TRYPSIN, TRYPSIN INHIBITOR AND TRYPSINOGEN LEVELS IN HUMAN PANCREATIC JUICE

Patient	State of Pancreas	Drainage	Spontaneous Tryptic Activity (μg./ml.)	Trypsin Inhibited per ml. Pancreatic Juice (μg./ml.)	Trypsinogen Activated* by Enterokinase (μg. of activated trypsin/ml.)
B. S.	Normal	Catheter	0	42	234
				92	218
				92	218
					101
H. K.	Mild subacute pancreatitis	Catheter	0	146	486
J. Q.	Normal	Catheter	0	153	257
				165	188
C. A.	Choledocholithiasis, mild pancreatitis	Catheter	0	...	...
S. N.	Choledocholithiasis	Catheter	...	150	267
R. T.	Traumatic pancreatic fistula	Fistula	0	48	24
A. B.	Traumatic pancreatic fistula	Fistula	0	99	0

* Trypsinogen levels were measured in amounts of activated trypsin in excess of inhibitor. It is therefore obvious that the level of trypsinogen is greater than the values listed above by that amount of trypsin bound to inhibitor.

and benzoylarginineamide hydrochloride in an oil bath to 150°C. The mixture is kept at this temperature for five minutes after melting occurs. After cooling the melt is washed repeatedly with 95 per cent ethanol to remove excess paranitroaniline; the mixture is then filtered and dried in a desiccator. A supersaturated aqueous solution of BAPNA in a concentration of 1 mg. per ml. is prepared by heating to 85°C. until dissolution is complete, and then cooling in an ice bath. The solution may be stored at room temperature for at least one month.

As buffer, 0.1 M Tris (hydroxymethyl) aminomethane, pH 7.7, was employed.

To prepare trypsin standards, lyophilized crystalline trypsin (Worthington Biochemical Corporation) was used. A stock standard of trypsin in a concentration of 1 mg. per ml. was prepared in 0.0025 N HCl. Working standard solutions of trypsin were prepared by diluting the stock standards to the desired concentration. The protein content of trypsin standards was determined by measuring absorbance at 280 mμ in the Beckman DU Spectrophotometer and using the conversion factor of 0.585 as described by Kunitz [8].

Enterokinase was obtained from human duodena which were slit longitudinally; after ultracentrifugation the supernatant was frozen and used as the source of enterokinase. This preparation has no lytic effect on BAPNA.

Pancreatic juice was obtained by catheter drainage of the duct of Wirsung in five human subjects and from two others with pancreatic fistulas. Three of the subjects had indwelling catheters for many days. In the other two, juice was obtained from the catheter just prior to a pancreatic ductogram. Of the five subjects with catheter drainage two had a pancreas described as normal at surgery, two had choledocholithiasis with mild pancreatitis, one had subacute pancreatitis. The cause of the pancreatic cutaneous fistulas in both subjects was trauma. (Table I.)

To determine tryptic activity of a solution, a small volume (usually in the order of 0.1 to 0.4 ml.) of the fluid containing the protease was added to a mixture of 1.5 ml. of BAPNA substrate and Tris buffer which had been incubated for ten minutes at 37°C. The amount of Tris buffer was calculated to provide a total volume of 3.0 ml. Activity was measured in the Beckman DU Spectrophotometer at 383 mμ.

EXPERIMENTAL

Measurement of Trypsin. In a 3 ml. BAPNA system, trypsin activity measured in Beckman O.D. units per minute is directly proportional to the amount of trypsin added. (Fig. 1.) When the change in optical density per minute is recorded, trypsin can be accurately assayed in the range of 1 μg. To increase the sensitivity, trypsin may be incubated with BAPNA and buffer for varying periods (twenty to thirty minutes) and the reaction stopped by the addition of 1 ml. of 0.2 N HCl. The total increase in optical density compared to blanks accurately assays trypsin in the range of 0.5 μg.

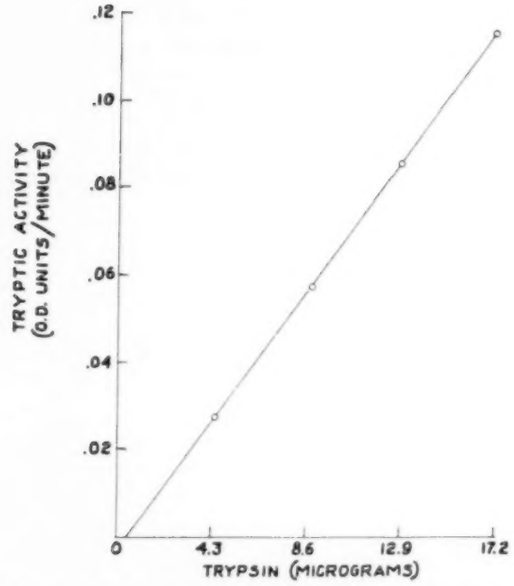


FIG. 1. The lytic effect of trypsin on the substrate benzoylargininеparanitroanilide. Tryptic activity is expressed in optical density units per minute. The measurements were made in the Beckman DU Spectrophotometer at 383 mμ.

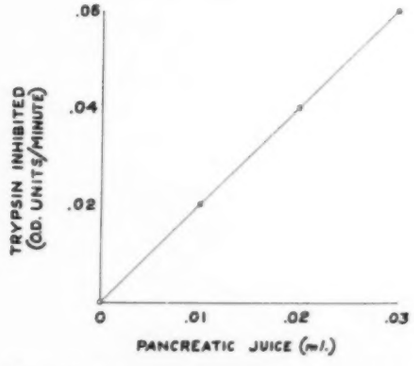


FIG. 3. A stoichiometric relationship exists between pancreatic juice inhibitor and trypsin.

BAPNA substrate is not affected by enterokinase, common duct bile, calcium ion, magnesium ion, chymotrypsin or a mixture of streptokinase-streptodornase (Varidase®).

Pancreatic Juice Inhibitor. The pancreatic juice obtained by catheter drainage from the five subjects and from the two with pancreatic fistulas exhibited no spontaneous tryptic activity. To determine trypsin inhibitor levels, trypsin in excess of the inhibitor was added to pancreatic juice. A mixture of 0.1 ml. of pancreatic juice and 0.1 ml. of trypsin solution (82 μg. per ml.) was incubated for various periods of time and excess trypsin was measured.

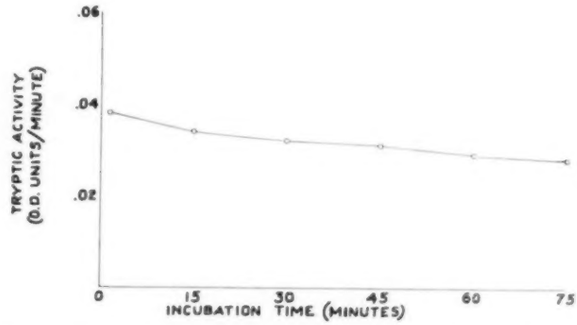


FIG. 2. The effect of trypsin on pancreatic juice inhibitor at time intervals. Trypsin in excess of inhibitor was added to pancreatic juice. It is noted that no digestion of pancreatic juice inhibitor occurs.

Inhibitor levels were expressed in micrograms of trypsin inhibited per milliter of juice. Pancreatic juice from all seven subjects demonstrated trypsin inhibitor. The values for the individual juices are illustrated in Table 1. The duration of incubation time did not affect the inhibitory action, indicating that the reaction between inhibitor and trypsin was rapid, and also that trypsin did not digest the inhibitor. (Fig. 2.) This experiment was repeated many times with identical results. It was also observed that trypsin and pancreatic juice inhibitor reacted stoichiometrically. (Fig. 3.) Presently, studies are in progress with trypsin inhibitor isolated from human pancreatic juice. The effect of enterokinase on this inhibitor is also being studied.

Activation of Trypsinogen in Pancreatic Juice. Trypsinogen in human pancreatic juice was not activated by the following: (1) exposure of pancreatic juice to room temperature for periods of time up to forty-eight hours; (2) incubation of a mixture of pancreatic juice, BAPNA and Tris buffer for periods of time up to forty-eight hours; (3) incubation with human bile obtained from the common duct via T-tube drainage for periods up to eight hours; (4) exposure of a mixture of pancreatic juice, common duct bile, BAPNA and Tris buffer for a period up to forty-eight hours; (5) incubation with 2,000 units of a mixture of streptokinase-streptodornase (Varidase) for periods up to seventy-two hours; (6) incubation with calcium chloride in concentrations from 10 mEq. per L. to 200 mEq. per L. for periods of time up to forty-eight hours; and (7) incubation of pancreatic juice, calcium ion in a concentration of 10 to 200 mEq. per liter, BAPNA, and Tris buffer for periods up to forty-eight hours at room temperature and

TABLE II

THE EFFECT OF VARYING THE CONCENTRATION OF ENTEROKINASE ON ACTIVATION OF TRYPSINOGEN TO TRYPSIN

TRYPTIC ACTIVITY (Δ O.D. UNITS/ML.)

	Minutes																
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Ml. Enterokinase 0.08		0.047	0.056	0.067	0.074	0.078	0.082	0.084	0.085	0.084	0.083	0.083					
Ml. Enterokinase 0.05		0.034	0.042	0.050	0.057	0.064	0.069	0.074	0.080	0.083	0.083	0.083	0.083	0.083			
Ml. Enterokinase 0.03		0.026	0.028	0.035	0.040	0.043	0.049	0.057	0.065	0.069	0.073	0.075	0.078	0.080	0.082	0.084	0.083

NOTE: The change in optical density per minute is recorded. It is noted that the time of maximal optical density change is inversely proportional to the concentration of enterokinase.

at 37°C. It should be pointed out, however, that when human pancreatic juice which had been frozen for several months was incubated with calcium ion in a concentration of 10 to 20 mEq. per L., slight tryptic activity was noted.

ENTEROKINASE ACTIVATION OF TRYPSINOGEN

To determine the activation of trypsinogen in juice by enterokinase, the following procedure was adopted. Pancreatic juice in an amount of 0.1 ml. was added to a mixture of 1.5 ml. of BAPNA and 1.3 ml. of Tris buffer. At time zero, 0.1 ml. of enterokinase was added and an increase in optical density was measured until a maximal change occurred. It is assumed that at this point all the trypsinogen has been converted. Trypsinogen activation by varying amounts of enterokinase is shown in Table II and Figure 4. Enterokinase actively converts trypsinogen to trypsin. It is noted that the initial activity (i.e., trypsin liberated in the first minute) is greater with larger amounts of enterokinase.

The effect of calcium ion on the conversion of trypsinogen to trypsin in juice by enterokinase was studied. Pancreatic juice was incubated with

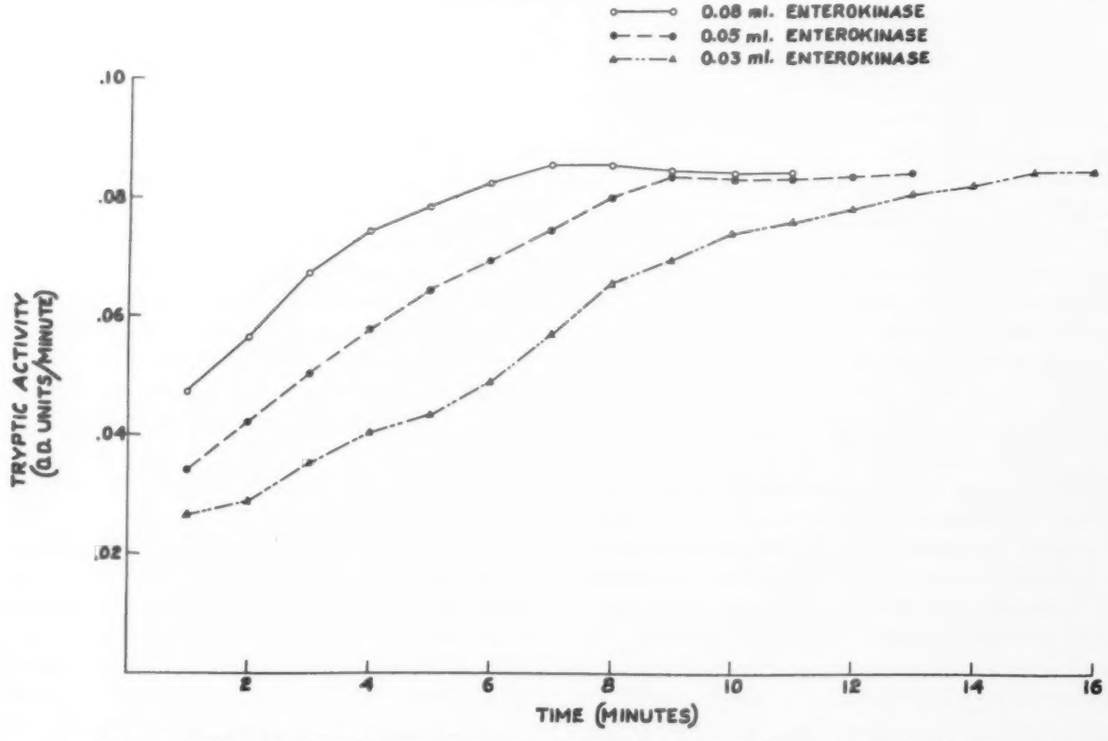


FIG. 4. Activation of trypsinogen in pancreatic juice by varying amounts of enterokinase.

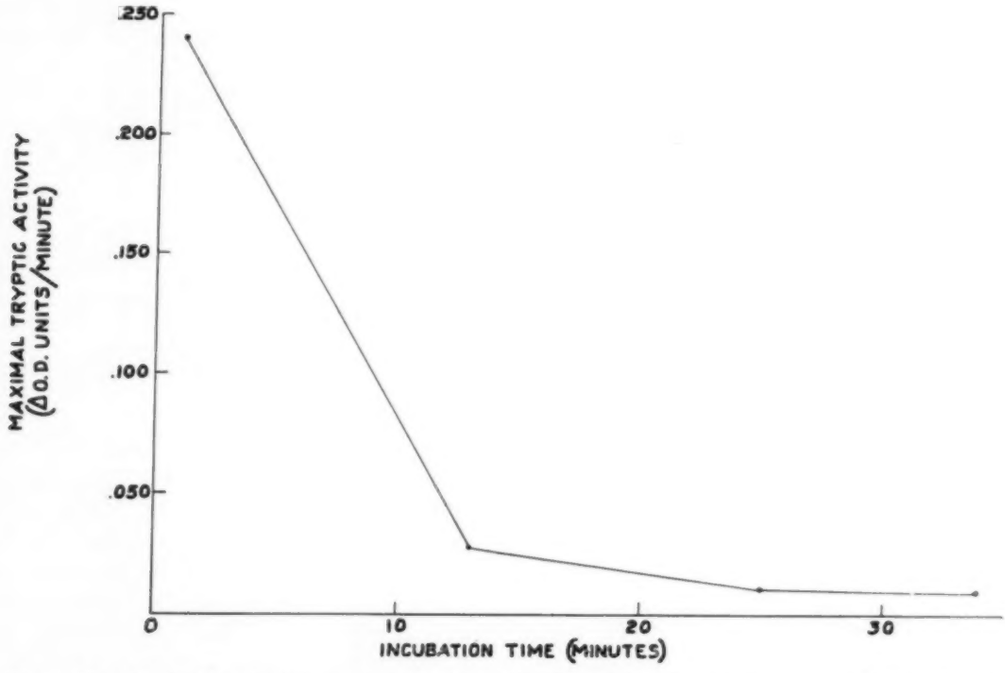


FIG. 5. The effect of incubating pancreatic juice with calcium ion in a concentration of 200 mEq./L. on conversion of trypsinogen to trypsin by enterokinase.

calcium ion in a concentration of 200 mEq. per L. At approximately ten minute intervals conversion of trypsinogen by enterokinase was determined in aliquots of this mixture as described. When the incubation of juice and calcium ion exceeded fifteen minutes, conversion was almost completely inhibited. (Fig. 5.) Calcium ion in concentrations of from 3 to 10 mEq. per L. had little or no effect.

AUTODEGRADATION OF TRYPSINOGEN

The problem of activation of trypsinogen to trypsin in pancreatic juice is complicated by the fact that this precursor undergoes degradation when allowed to remain at room temperature or when incubated at 37°C. This was determined by converting the precursor to trypsin at varying time periods with enterokinase. When undiluted pancreatic juice is allowed to incubate at 37°C. for forty-five minutes, approximately half of the trypsinogen has been destroyed. This degradation occurs despite the absence of any measurable tryptic activity. When pancreatic juice is diluted with Tris buffer (1:1 ratio), the degradation of trypsinogen is more rapid. The addition of calcium ion in a concentration of 3 mEq. per L. retards the degradation by approximately 80 per cent. (Fig. 6.)

ACTIVATION OF TRYPSINOGEN BY TRYPSIN

To determine whether or not trypsin autocatalyzes trypsinogen in pancreatic juice, the following experiments were performed. A mixture of 1 ml. of pancreatic juice and 1 ml. of bovine trypsin (100 μg. per ml.) was incubated at 37°C. At fifteen minute intervals, for a period up to eight hours, 0.2 ml. of the mixture was tested for tryptic activity. The trypsin concentration was varied from 55 to 110 μg. per ml., but at all times was in excess of the inhibitor level. When pancreatic juice was first diluted with Tris buffer in a 5:4 ratio respectively, the addition of bovine trypsin did not activate the trypsinogen. The concentration of calcium ion naturally occurring in this juice was 1.8 mEq. per L. However, when calcium was added to pancreatic juice in as small a concentration as 1.3 mEq. per L. a small amount of trypsinogen was catalyzed to active trypsin. The addition of calcium ion in a concentration of 2 mEq. per L. considerably increased the conversion of trypsinogen to trypsin. With greater amounts of calcium ion the conversion of trypsinogen to trypsin was markedly increased. (Fig. 7.) When bovine trypsin was added to undiluted pancreatic juice in one instance very slight conversion of trypsinogen to trypsin occurred.

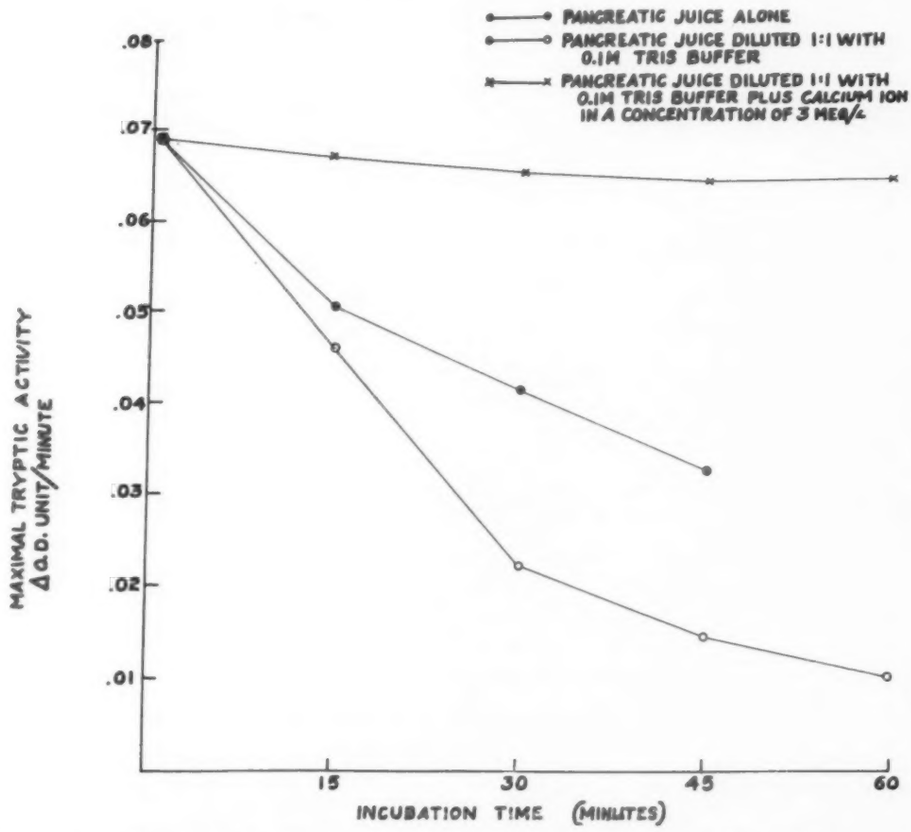


FIG. 6. Autodegradation of trypsinogen. At fifteen-minute intervals trypsinogen is converted to trypsin by enterokinase.

Using other specimens of pancreatic juice, no activation occurred.

At this point it was desirable to determine whether or not human trypsin could activate trypsinogen in human pancreatic juice. Pancreatic juice containing active trypsin (calcium concentration 1.35 mEq. per L.) but no enterokinase was added to pancreatic juice containing trypsinogen but no active trypsin (calcium concentration 0.95 mEq. per L.). The amount of active trypsin exceeded the trypsin inhibitor level. Conversion of trypsinogen to trypsin occurred in a very modest amount. However, when potassium oxalate was added to remove calcium ion and the experiment repeated, no activation of trypsinogen occurred. (Fig. 8.)

The effect of trypsin on trypsinogen in human pancreatic juice without the addition of calcium was investigated next. It became of interest to determine whether or not trypsin converted trypsinogen in human juice to inert protein when no calcium was added. To determine this effect, the trypsinogen levels of 0.1 ml. of pancreatic juice were measured at fifteen minute intervals for one hour with and without the addition of 5.5 μg. of bovine trypsin per 0.1 ml. of pancreatic juice. This quantity of trypsin provided an excess after saturating the inhibitor. At the desired times trypsinogen was activated to trypsin by enterokinase. The results of this study indicate that when trypsin is added to pancreatic juice with no additional calcium ion, trypsinogen is usually converted to inert protein rather than to active trypsin. (Fig. 9.)

COMMENTS

As trypsin has an important role among the pancreatic proteases, it is likely that the mechanism forming this enzyme from its precursor within the pancreas is involved in the etiology of acute pancreatitis. The many studies in which purified enzyme systems were used may not be wholly applicable to the mixtures of substances found within the acinous cell or in the pancreatic juice. Although interpretation of the results may be more difficult under these circumstances,

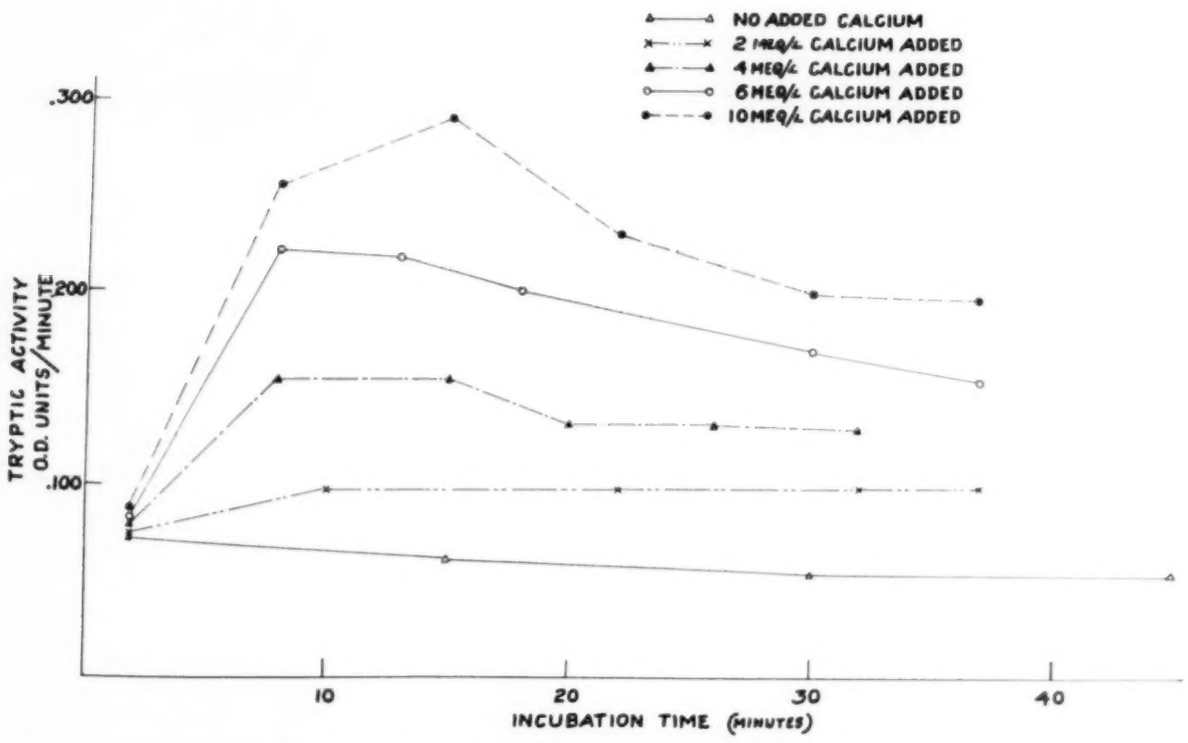


FIG. 7. The effect of calcium ion on the activation of trypsinogen in pancreatic juice by bovine trypsin. Pancreatic juice, trypsin and varying concentrations of calcium were incubated and aliquots removed periodically and assayed for tryptic activity. Trypsin was added in amounts that exceeded the inhibitor level.

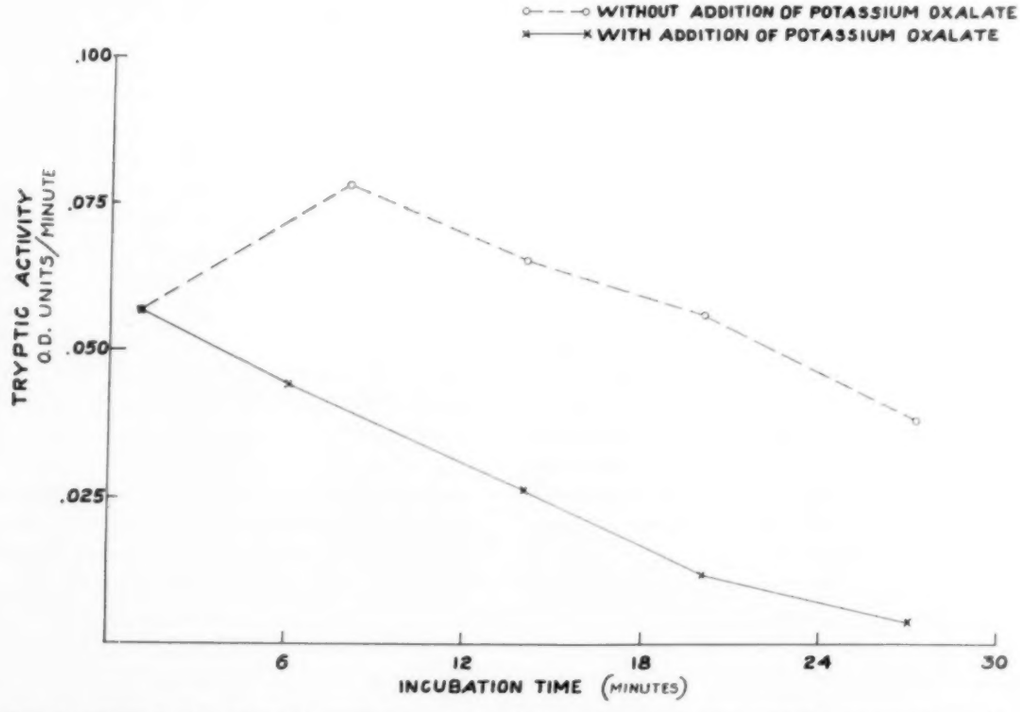


FIG. 8. The activation of trypsinogen in pancreatic juice by human trypsin added in excess of tryspin inhibitor level. When potassium oxalate was added to remove calcium ion no activation of trypsinogen occurred.

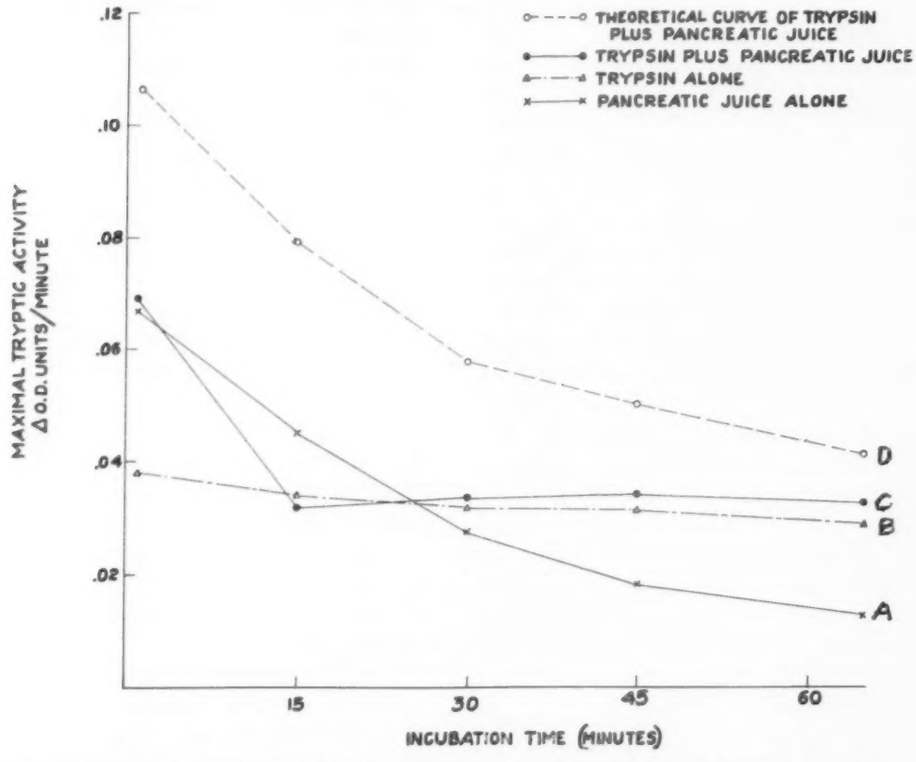


FIG. 9. The effect of bovine trypsin on trypsinogen in pancreatic juice without the addition of calcium. At fifteen-minute time intervals the trypsinogen in pancreatic juice was activated by enterokinase and measured. Curve A represents the autodegradation of trypsinogen in pancreatic juice at time intervals. Curve B represents the degradation of trypsin alone. Curve C represents the degradation of trypsinogen in pancreatic juice when trypsin is added. It is noted that trypsinogen degradation is increased when trypsin is added. Curve D illustrates the theoretical levels of trypsinogen in pancreatic juice with added trypsin if no activation or degradation of trypsinogen by trypsin occurred.

studies in which whole pancreatic juice was assayed may elucidate happenings closely related to the problem *in vivo*.

Human pancreatic juice aspirated directly from the duct of Wirsung has no spontaneous tryptic activity. It does, however, contain substantial amounts of trypsin inhibitor. These findings explain the absence of skin digestion around cutaneously draining pancreatic fistulas in many subjects. The importance of the role of trypsin inhibitor in pancreatic juice has not been clearly defined. One could suppose that pancreatic trypsin inhibitor is present to inactivate any trypsin released from its precursor within the gland or within the duct system. However, Grossman [*9*] has shown in the rat that trypsin inhibitor, at least that fraction soluble in trichloracetic acid, was digested by both trypsin and chymotrypsin. It is evident that the trypsin inhibitor in human pancreatic juice, which also is soluble in trichloracetic acid, is not destroyed by trypsin and chymotrypsin. There is either a difference in species or in extraction procedures to account for the discrepancy. From a theoretical point of view, it is desirable to have a trypsin inhibitor which will not be destroyed by trypsin or chymotrypsin.

The mechanism of activation of trypsinogen to trypsin within the pancreas or in pancreatic juice remains an enigma. However, the present studies have indicated that human bile and a mixture of streptokinase-streptodornase do not activate trypsinogen. It was surprising to ascertain that crystalline trypsin, in excess of the amount required to saturate the inhibitor, usually did not catalyze the conversion of trypsinogen to trypsin. This was true for both human and bovine trypsin. In a few instances incubation of human trypsin with undiluted pancreatic juice activated small amounts of trypsinogen to trypsin. Calcium ion alone when added to pancreatic juice in concentrations from 10 to

200 mEq. per L. did not activate pancreatic trypsinogen. However, slight tryptic activity was noted in human juice, which had been frozen for several months, when incubated with calcium ion. The prior addition of calcium ion in amounts as small as 1.3 mEq. per L. to pancreatic juice permitted activation of a small amount of trypsinogen to trypsin by trypsin. When greater concentrations of calcium ion were added more trypsinogen was activated by the same amount of trypsin. This indicates that the activation of trypsinogen to trypsin is controlled in a direct manner by the amount of calcium ion present. Within limits the greater the amount of calcium ion the greater the activation.

This relationship would indicate that with calcium ion in normal concentration little or no activation of trypsinogen by trypsin would occur in human pancreatic juice. Also, if the calcium ion concentration and free trypsin relationship permitted conversion of only a small amount of trypsinogen, trypsin inhibitor would inactivate the trypsin released and thus prevent the unleashing of uncontrolled trypsinogen conversion. It becomes apparent that in pancreatic juice and likely within the acinous cell there are systems of checks to prevent conversion, or at least the uncontrolled conversion, of trypsinogen to trypsin. Magnesium, barium and ammonium ions did not convert trypsinogen to trypsin. Neither did acidification of pancreatic juice to a pH of 4.5.

Calcium ion has other interesting actions in the complex mechanism producing active trypsin. They are as follows: (1) This ion protects trypsin from autodigestion. This has been documented by many investigators as well as in the studies presented herein. (2) Trypsinogen capable of being activated decreases with time when pancreatic juice is incubated at 37°c. Calcium ion substantially slows the rate of degradation. It would be important to determine the factor or factors responsible for the degradation and the role that calcium assumes in preventing this reaction. One could speculate that a proteolytic reaction involving a protease other than trypsin splits trypsinogen to inert protein and that calcium protects the precursor from this action. (3) It has been postulated that calcium ion enhances the conversion of trypsinogen to active trypsin rather than to inert protein [*8*]. That this hypothesis hold true for the conversion of trypsinogen in human pancreatic juice is evident from these studies. We note that when human pancreatic juice is incubated with crystalline bovine trypsin or human trypsin, little or no activation occurs. Without additional calcium ion, trypsin may increase the degradation of trypsinogen. It would appear, therefore, that within the pancreas, even if free trypsin were available, little or no catalysis of trypsinogen would occur. Once again, we observe mechanisms guarding against the release of active trypsin.

From these data the following over-all pattern emerges. Within the pancreas are inherent safeguards to prevent the production of trypsin in an active form. These mechanisms are (1) trypsin destroys trypsinogen (2) trypsin digests itself (3) autodegradation of trypsinogen by a mechanism that has no measurable active trypsin (4) trypsinogen is autocatalyzed to trypsin in a controlled fashion (5) trypsin inhibitor is present to inactivate substantial amounts of the active protease.

Interestingly enough, calcium ion enhances the formation of active trypsin by inhibiting the first three mechanisms and enhancing the fourth. Also, this ion is effective in these roles in small amounts. Common to all four mechanisms is trypsin, either in an active state or in precursor form. It is likely, therefore, that calcium ion affects this molecule, but in what precise manner is not known. Calcium ion is essential for the conversion of prothrombin to thrombin, another proteolytic reaction. The active site of thrombin is chemically similar to that of trypsin. As calcium ion increases the amide-splitting action of thrombin-on-BAPNA, once again it is likely that calcium affects thrombin in a manner similar to trypsin.

Both acute and chronic pancreatitis have been associated with hyperparathyroidism and some patients have demonstrated pancreatic calcification. The occurrence of hypercalcemia in hyperparathyroidism often increases the serum calcium levels to a range sufficient for the enhancement of factors leading to active trypsin. It is suggested that these factors may play a significant role in the association of these two diseases.

SUMMARY

1. Benzoylarginine-paranitroanilide was employed as substrate in a method which permits simple, sensitive and rapid assay of trypsin.

2. Human pancreatic juice obtained by

catheter drainage of the duct of Wirsung exhibited no spontaneous tryptic activity. It does, however, contain substantial amounts of spontaneous trypsin inhibitor. Human pancreatic juice inhibitor, which is soluble in trichloracetic acid, is not digested by trypsin.

3. Trypsinogen in human juice is not activated by incubation with bile, streptokinase-streptodornase, calcium ion, magnesium ion, barium ion, ammonium ion, or acidification of juice to a pH of 4.5. Bovine or human trypsin does not activate or only slightly activates trypsinogen in human pancreatic juice. However, the addition of small amounts of calcium markedly enhances the conversion of trypsinogen to trypsin by trypsin. Slight tryptic activity was noted in human juice, which had been frozen for several months, when incubated in calcium ion.

4. Trypsinogen in juice undergoes autodegradation even though no measurable trypsin is present. Calcium ion retards this reaction. In many instances addition of trypsin to pancreatic juice enhanced degradation of trypsinogen.

5. Enterokinase actively converts trypsinogen in juice to trypsin. The time of maximal conversion is inversely proportional to the amount of enterokinase.

6. Calcium ion enhances conversion of trypsinogen to trypsin in pancreatic juice in many ways. These may explain the association of pancreatitis with hyperparathyroidism.

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Value of Splenic Portography in the Diagnosis of Intrahepatic and Extrahepatic Neoplasm*

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DURING the course of a study of the portal venous system in cirrhosis by means of splenic portography [*1*], several patients with intrahepatic and extrahepatic carcinoma were examined by this roentgen method. A number of authors [*2,5,7,8,9,12,14,15*] have described the application of portography (including splenic, portal and transaortic portography) to the diagnosis of both intrahepatic and extrahepatic carcinoma but the combined experience remains relatively small. Therefore, it was considered to be worth while, to record our own observations of thirteen cases so studied.

Full details of the technic of splenic portography have been given elsewhere both by our group [*11,13*] and by others [*1,2,7,8*]. Therefore, a brief description of this aspect of the examination will suffice in this report. In this study, 40 cc. of Urokon® Sodium (70 per cent) was injected into the spleen in about twelve seconds (range of ten to fifteen seconds), and films were obtained at two, four, six, eight, twelve, sixteen, twenty, twenty-four, twenty-eight and thirty-two seconds after the start of the injection. The final three films were exposed at thirty-seven, forty-two and sixty seconds. (Following completion of this study, a routine technic has been set up in which films are exposed at the following intervals: two, four, six, eight, twelve, sixteen, twenty-four and thirty-two seconds.)

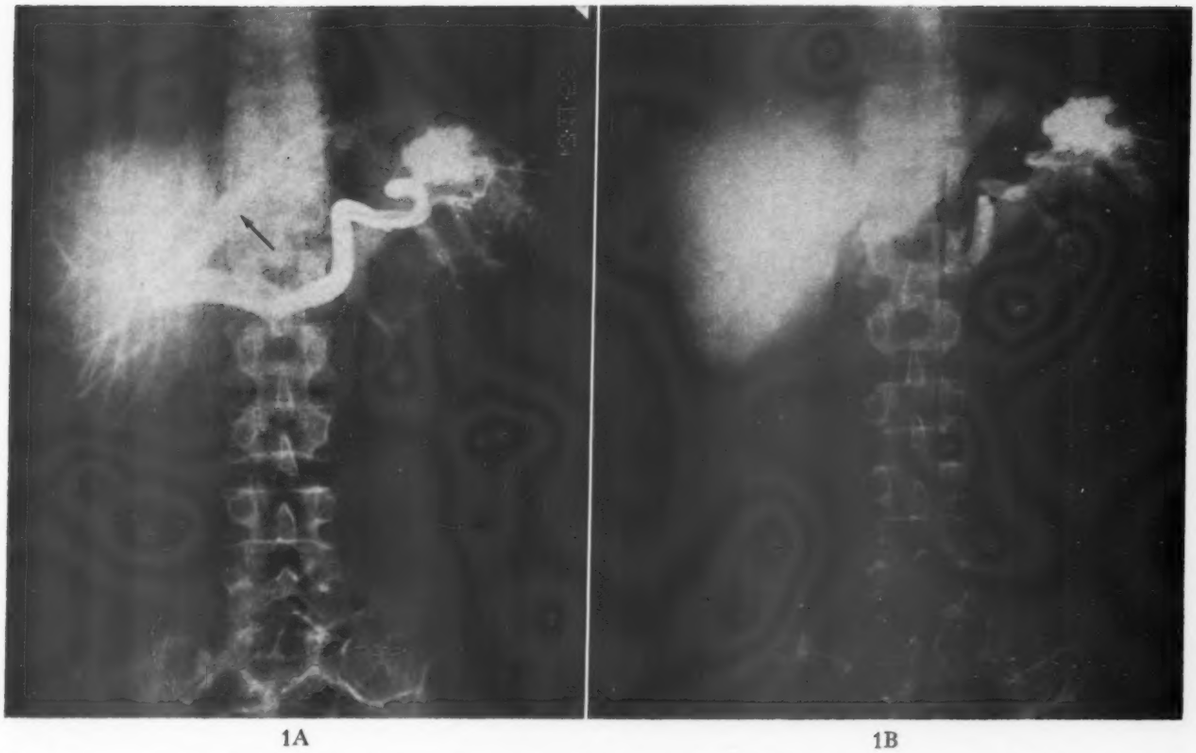
Following the intrasplenic injection, the extrahepatic vessels are filled first. Normally, blood flows directly from the site of injection through the splenic vein and portal vein to the liver. In the presence of obstruction of the portal venous system, there are various circuitous routes to carry blood over collateral veins to the systemic circulation in a hepatofugal direction. The majority of such obstructions are intrahepatic or extrahepatic (suprahepatic obstructions rarely are studied). If extrahepatic obstruction is complete, opacification of the liver is impossible unless bridging collaterals span the obstructed vessel and carry the opaque medium to the liver.

By means of serial percutaneous splenic portography it has been possible to visualize the liver in two major phases. The first, the vasculogram phase (Fig. 1A), consists of visualization of the intrahepatic portal vein branches, principally those of the right main branch. A normal intrahepatic portal venous tree shows symmetrical arborization, with branches evenly distributed. The branching vessels gradually diminish in size in succeeding orders of division, and there is a full complement of small and fine end vessels. Normally, the intrahepatic vasculogram is best demonstrated under the conditions of the technic employed from two to twelve seconds after the injection is begun, but may be visualized somewhat longer. The branches of the right lobe are regularly opacified when the patient lies in the supine position. The branches of the left lobe are frequently only partially opacified or may not be opacified at all. This phenomenon is related chiefly to layering of the opaque medium, which has a greater specific gravity than that of blood [*3*]. As a result, there normally occurs preferential filling of the right main intrahepatic branch, which is more posterior and therefore more dependent with the patient supine. It is sometimes possible to visualize the branches of the left lobe (as well as the right) by placing the patient in a slightly left posterior oblique position.

The second phase of liver visualization,

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1A 1B

FIG. 1. A, normal intrahepatic vasculogram. Exposure made at eight seconds. Note that branches of the left lobe of the liver are incompletely filled (arrow). B, hepatogram phase of liver opacification (taken at 20 seconds). The density varies normally from 3 plus to 4 plus. The left lobe is less dense than the right but the inferior margin can be seen.

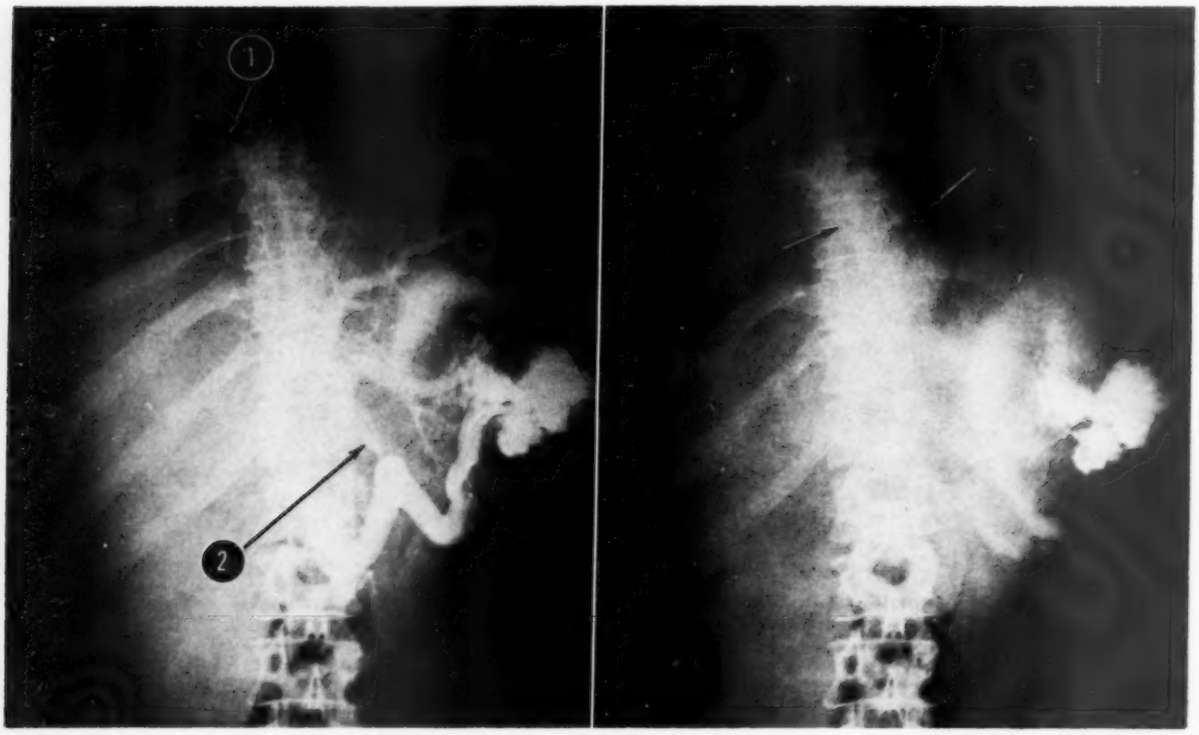
termed the hepatogram, consists normally of a diffuse homogeneous opacification, probably due to filling of liver sinusoids with opaque medium. (Fig. 1B.) This is in contrast to the mechanism of opacification that occurs with thorium dioxide. The homogeneous opacification with the latter is produced by pickup of thorium dioxide by the reticuloendothelial system of the liver. Since the opaque medium employed in the present technic passes rather quickly through the vascular system of the liver, and since opacification of sinusoids would be expected to produce a diffuse blush of density because of multiplicity and generalized distribution of the sinusoids, this is the most likely explanation of the hepatogram phase. This point, however, has not been experimentally proven.

Normally the hepatogram phase takes place following or concomitant with the latter part of the vasculogram. It begins usually ten to twelve seconds after the injection is started, and reaches a maximum at sixteen to twenty-four seconds. It may persist for as long as sixty seconds, although usually it fades considerably by thirty-seven to forty-two seconds. Late films are especially useful in patients in whom extrahepatic obstruction exists, under which circumstances the opaque medium reaches the liver later than normal after passing over bridging collaterals.

During the course of more than 250 serial splenic portograms performed predominantly on cirrhotic patients using the technic described, thirteen cases of carcinoma (Tables I and II) involving the liver or other organs in the upper part of the abdomen were encountered. Of the thirteen patients studied, ten had involvement of the liver. Of these ten patients, two were primary in the liver, seven were metastatic to the liver, and one involved liver by direct exten-

TABLE I
PATIENTS WITH CARCINOMA STUDIED BY SPLENIC PORTOGRAPHY

Location and No. of Primary Carcinomas	
Liver	2
Gallbladder	2 (one extends directly to the liver)
Pancreas	5 (three metastatic to the liver)
Stomach	2 (metastatic to the liver)
Rectum	1 (metastatic to the liver)
Eye (melanoma)	1 metastatic to the liver)



2A 2B

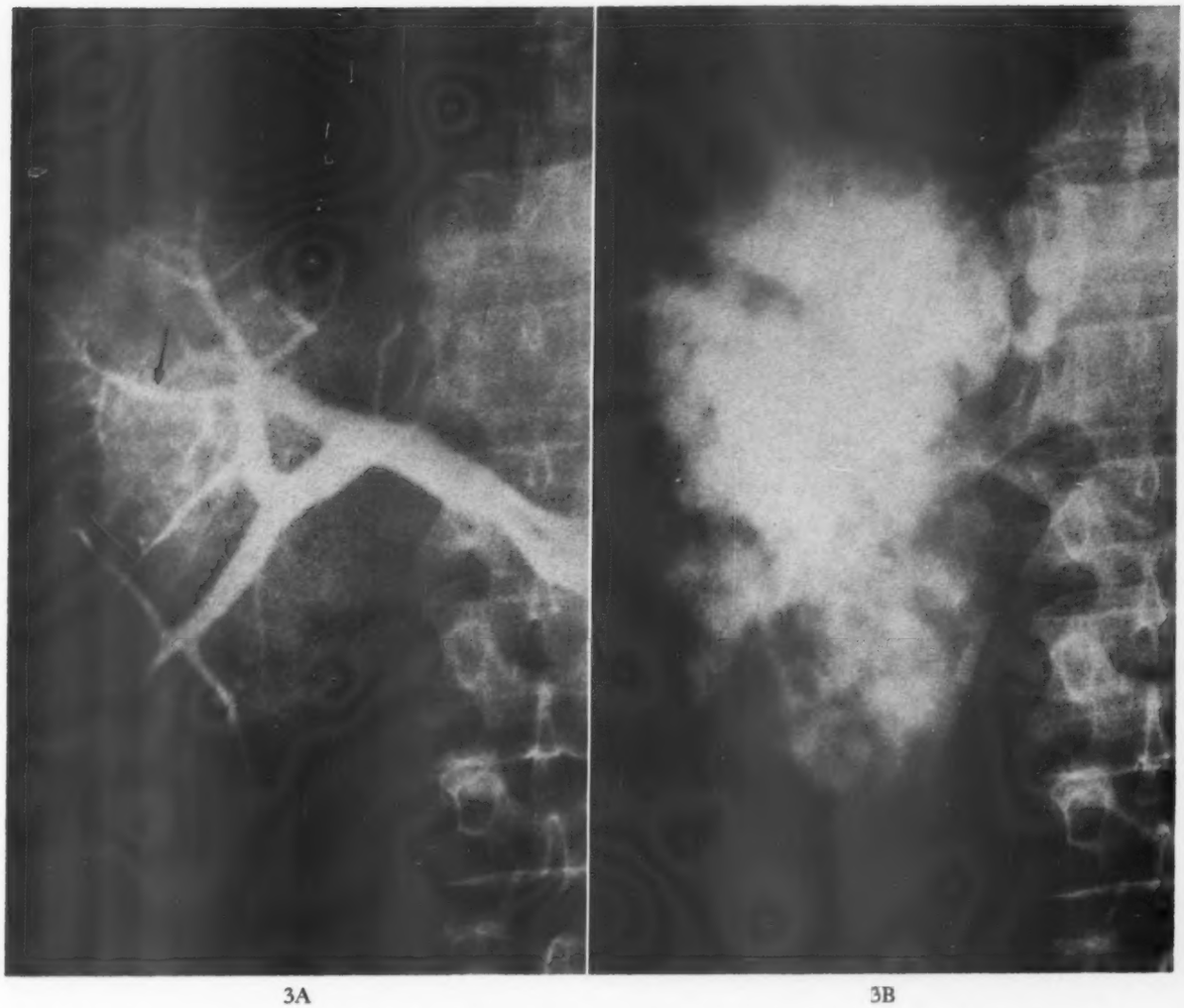
FIG. 2. A, vasculogram phase (eight seconds). A massive primary neoplasm occupies almost all of the right lobe of the liver (diagnosis established at surgery and postmortem examination). Note (1) several displaced vessels of the right lobe. The opaque medium is directed in relatively large measure into the branches of the left lobe. There is compensatory enlargement of the left lobe, the inferior margin (2) of which superimposes immediately above the splenic vein. B, hepatogram phase (twenty-four seconds). Just as no intrahepatic portal vessels are visualized in the area of the tumor, no hepatogram (increased density) is seen in the area of the tumor. However, the remaining portion of the right lobe shows a moderately dense hepatogram (between arrows). The left lobe is faintly opacified. At postmortem examination, two weeks after the portogram, two nodules (1.5 cm. and 2 cm. in diameter) were found in the left lobe. These are not identified in the hepatogram.

sion from a primary carcinoma of the gallbladder. In nine of the total of thirteen cases the primary lesion was in the upper quadrant of the abdomen, but arose in organs other than the liver: five in the pancreas, two in the gallbladder and two in the stomach.

PRIMARY CARCINOMA OF THE LIVER

As is well known, primary carcinoma of the liver may present as a solitary large tumor mass, sometimes surrounded by a few satellite nodules. Other patterns, of multiple scattered nodules or of more diffuse involvement, also occur. This lesion involves the right lobe of the liver more than the left [*4*]. Metastatic disease from primary carcinoma of the liver may appear in adjacent lymph nodes about the liver hilum, as well as in portal, mesenteric and retroperitoneal lymph node areas. The tumor may also extend in retrograde fashion in portal vein. As a sequel to such tumor spread, or due to expansion of the liver itself, encroachment upon the portal vein may cause extrahepatic obstruction.

There are two proven cases of primary carcinoma of the liver in our series, both of hepatoma. In one, a solitary mass occupies most of the right lobe of the liver. (Fig. 2A.) The intrahepatic portal branches arch about the tumor and show a distinct displacement, compression effect. Because of considerable obstruction to the branches of the right lobe, the branches of the left lobe are fairly well filled. In the hepatogram phase (Fig. 2B) the tumor area fails to opacify, whereas the uninvolved remaining part of the right lobe shows a normal homogeneous increase in density. At the same time the enlarged left lobe displays a slight increase in density. This liver presented some periportal fibrosis at postmortem examination, but not a definite cirrhosis. In spite of the



3A 3B

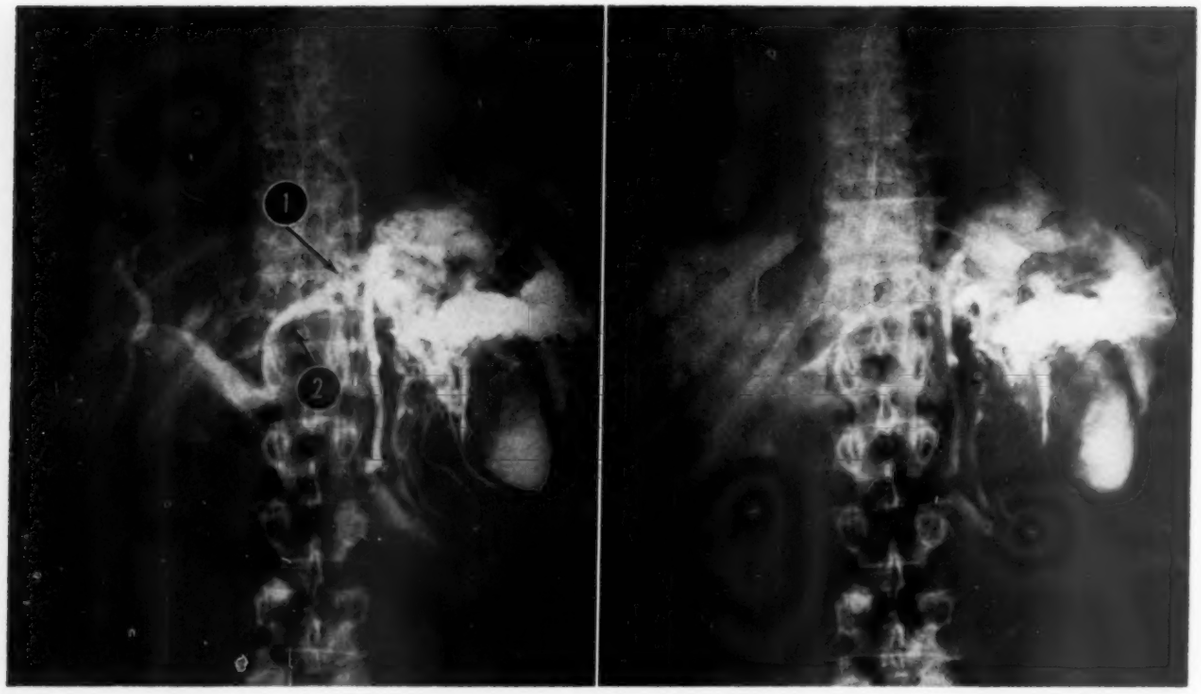
FIG. 3. Extensive metastatic disease in the liver from carcinoma arising in the pancreas (body and tail extensively involved at postmortem study). A, (vasculogram phase taken at 4 seconds) compression and displacement effects can be noted (arrows). Note that the vessels of the left lobe do not visualize. B, the hepatogram (taken at 16 seconds) reveals multiple radiolucent defects in the opacified liver due to carcinomatous nodules varying in size from less than 1 cm. to 4 cm. in diameter. The large shaft-like defect in the superiorlateral portion of the right lobe is believed to be the site of a recent liver biopsy (needle).

extensive lesion in the right lobe of liver, the degree of intrahepatic obstruction (corrected splenic pulp pressure, 362 mm. saline solution) was sufficient to result in only minimal hepatofugal venous flow. Only one small splenoretroperitoneal collateral was seen.

In the second case of primary carcinoma of the liver neither the vasculogram nor the hepatogram phase of liver opacification occurred because of complete extrahepatic obstruction of portal vein by a tumor thrombus. Collateral vein visualization occurred in the extrahepatic portal system. At postmortem examination, extensive replacement of the upper portion of the right lobe of the liver was found. Roentgenologically this was not visible because of the failure to obtain vasculogram or hepatogram. This hepatoma occurred as a concomitant of cirrhosis.

METASTATIC CARCINOMA

In metastatic carcinoma of the liver the lesions are likely to be multiple although of course, single metastases do occur. When small, that is, 3 cm. or less, they are not likely to produce obvious alterations in the vasculogram pattern. Thus it is possible for much of the liver to be replaced by metastatic nodules of this dimension and yet the vasculogram may appear relatively normal. This, it would seem, is due to



4A 4B

FIG. 4. Patient with carcinoma of body and tail of pancreas and extensive liver metastasis. A, vasculogram phase at twenty seconds. The splenic vein is completely obstructed by tumor. The opaque medium reaches the liver via short gastric veins from the spleen to gastric varices (1), and thence through the coronary vein (2) to the portal vein. Because of the decreased amount of medium reaching the intrahepatic portal branches, the vasculogram is difficult to evaluate. B, the hepatogram phase, however, shows multiple metastatic lesions (radiolucent defects in opacified liver) quite clearly in spite of the small delivery of opaque medium (film exposed at thirty-two seconds).

insufficient vascular obliteration or displacement effect. When large lesions are present a compression and/or displacement effect upon the intrahepatic portal vessels is more likely to be visible (Fig. 3A). The "thorn" sign [*6*], although infrequently present, is particularly helpful in this regard. When this sign is present, the vessel involved (a large or medium-sized vessel) assumes the appearance of a long thorn, the result of compression with complete flattening and obliteration of the vessel at the point of the thorn.

It is in the hepatogram phase, however, that splenic portography finds its most effective application in the demonstration of metastatic lesions. When sufficient opaque medium reaches the liver and sinusoidal filling is achieved lesions in the range of 1 cm. in diameter may be identified if multiple (Fig. 3B), and a single lesion of 1.5 to 2 cm. may be fairly easily seen. Larger lesions are quite readily delineated. Even in the hepatogram, delayed by extrahepatic obstruction (Fig. 4), relatively small lesions may at times be demonstrable. (On the negative side it is our opinion that the hepatogram must be moderately radiodense before absence of an intrahepatic lesion can be assumed.)

PRIMARY EXTRAHEPATIC CARCINOMA

Carcinoma Arising in Upper Quadrant of the Abdomen. Carcinoma arising outside of the liver, as from the gallbladder or head of the pancreas, may be suggested by splenic portography. We have studied, as previously related, nine patients with carcinoma arising from a site in the upper part of the abdomen other than the liver. (Table II.) Of these, two showed no deformity of the splenic or portal veins. In one of these two patients extensive carcinoma of the body and tail of the pancreas was found. In this case the extensive degree of liver metastasis produced no intrahepatic obstruction (as judged by collateral vein visualization). The other patient that showed no deformity had carcinoma of the stomach; there was no evidence of intrahepatic obstruction although the hepatogram showed several large metastatic lesions. The remaining seven patients showed definite deformity of

TABLE II

DETAILED ANALYSIS OF PATIENTS STUDIED

Case, Age (yr.), Sex	Diagnosis	Extent of Disease at Surgery	Extent of Disease at Autopsy	Deformity of Splenic and/or Portal Veins	Splenic Pulp Pressure (mm. saline)	Collaterals	Vasculogram	Hepatogram	Hepatomegaly (clinical)	Splenomegaly at Time of Portogram		Splenomegaly on Follow-up Examination
										Clinically	Roentgenologically	
E61807, 64, M	Carcinoma, stomach	Entire left lobe of the liver replaced and multiple large right lobe metastases	No autopsy	0	140	0	Positive	Positive	0	0	0	No follow-up examination
E63517, 66, M	Carcinoma, body and tail of pancreas	No surgery	Massive involvement of both upper quadrants (including the liver) one month after portogram	0	230	+	Positive	Positive	+	0	0	0 (one month later postmortem examination)
1-00-86, 62, M	Carcinoma, stomach, recurrent	Single liver metastasis (1.5 cm. in diameter)	No autopsy	+	148	0	Negative	Positive	0	0	0	No follow-up examination
E61002, 46, M	Carcinoma, body and tail of pancreas	Many discrete liver metastases up to 2 cm. in diameter	No autopsy	+ (complete obstruction splenic vein)	380	+	Not diagnostic	Positive	+	+	+	No follow-up examination
E45179, 62, M	Carcinoma, body and tail of pancreas	Single metastasis in dome of liver	Tumor in dome of right lobe of liver, left periadrenal and peripancreatic lymph nodes	+ (complete obstruction splenic vein)	277	+	None	None	+	0	+	+ (at autopsy 3 days after portogram)
E49147, 47, F	Carcinoma, gallbladder	Disease unrecognized, grossly limited to gallbladder wall microscopically. Surgery 4½ months before portogram	Infiltrating gallbladder bed 2½ months after portogram	+	225	Borderline	Negative	Positive	0	0	0	+ (at autopsy 2½ months after portogram)
E39050, 55, F	Carcinoma, gallbladder	Gallbladder largely replaced by tumor. Stony hard areas in portal, no metastases in liver, surgery and portogram April, 1956	Right lobe metastases (six months after portogram)	+ (complete obstruction portal vein)	No pressure	+	Not diagnostic	Not diagnostic	0	0	+	+ (at surgery 1 week after portogram)
E22526, 76, M	Carcinoma, tail of pancreas	No surgery	No liver metastasis. 6 by 6 by 6 cm. mass arising in tail of pancreas and spreading to surrounding viscera 2 weeks after portogram	+ (complete obstruction splenic vein)	303	+	Negative	Negative	0	0	+	+ (2 weeks after portograms, postmortem)
E55197, 45, F	Carcinoma, head of pancreas	Obstruction common duct, cystic duct and portal vein by tumor, no metastases found	No autopsy	+ (partial obstruction portal vein)	90	+	Negative	Negative	+	0	Border line	+ (at laparotomy 1 week prior to portogram)

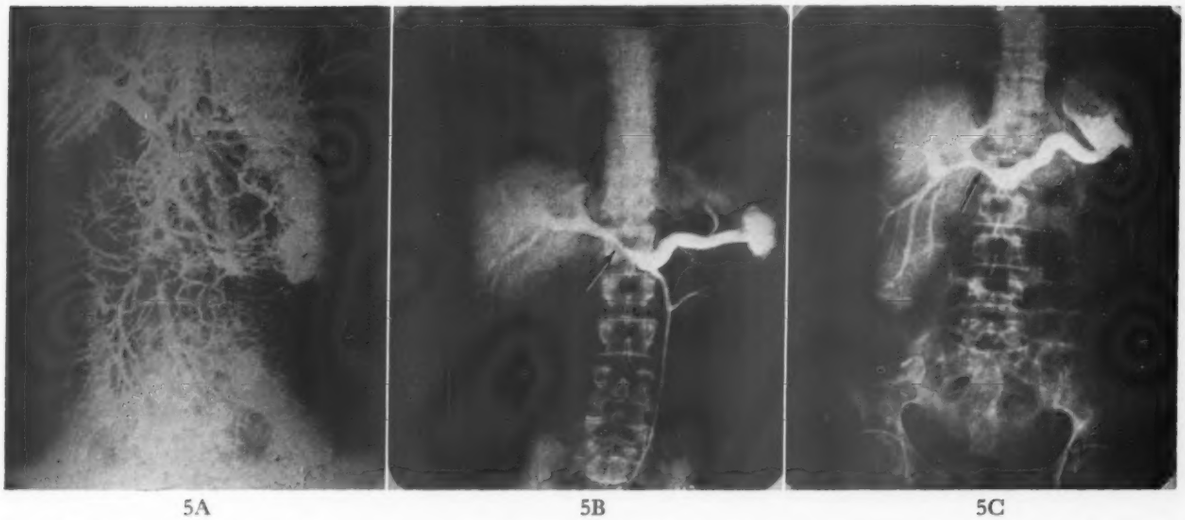
TABLE II (*Continued*)
DETAILED ANALYSIS OF PATIENTS STUDIED

Case, Age (yr.), Sex	Diagnosis	Extent of Disease at Surgery	Extent of Disease at Autopsy	Deformity of Splenic and/or Portal Veins	Splenic Pulp Pressure (mm. saline)	Collaterals	Vasculogram	Hepatogram	Hepatomegaly (clinical)	Splenomegaly at Time of Portogram		Splenomegaly on Follow-up Examination
										Clinically	Roentgenologically	
E63654, 49, M	Melanoma (primary in eye 15 years previously)	Many small liver metastases	No autopsy	0	245	Border line	Negative	Positive	+	0	Border line	No follow-up examination
E76160, 45, F	Carcinoma of sigmoid colon, resected 3 years prior to portogram	No surgery at time of portogram	No autopsy	0	380	+	Positive	Positive	+	0	0	No follow-up examination
E69308, 51, F	Hepatoma	Massive right lobe tumor	Three metastases in left lobe one month after portogram	0	362	Border line	Positive right lobe	Positive right lobe	+	+	+	+ (one month later at postmortem examination)
E62205, 45, M	Hepatoma	No surgery	Scattered areas of tumor, right dome of liver extending to portal vein (one week after portogram)	+ (complete obstruction portal vein)	340	+	None	None	+	0	0	+ (at postmortem one week after portogram)

portal and/or splenic veins. Two of these seven (with carcinoma of the stomach and carcinoma of the gallbladder) showed deformity of veins without definite evidence of obstruction and both had a diagnostic hepatogram. In one patient with carcinoma of the head of the pancreas there was an extrinsic pressure deformity with incomplete obstruction of the extrahepatic portal vein; a diagnostic hepatogram was achieved in this case of extrahepatic obstruction. Fou of the seven patients had complete extrahepatic obstruction of portal or splenic veins. These were two cases of carcinoma of the body and tail of the pancreas, one case of carcinoma of the tail of the pancreas, and one case of carcinoma of the gallbladder. Of the four, two had a diagnostic hepatogram with the aid of bridging collaterals, one presented a non-diagnostic hepatogram and one gave no hepatogram at all. Thus of the total of nine cases of primary extrahepatic carcinoma reviewed, seven had hepatograms which were considered to be diagnostic.

Carcinoma of the gallbladder and of the head of the pancreas may give very similar findings. Characteristic among our patients has been a smooth concentric narrowing of the portal vein (Fig. 5) which may or may not produce obstruction. In all patients (three in this series and one at postmortem examination [Fig. 5A]) in whom carcinoma of the gallbladder or head of the pancreas caused portal vein deformity, there was no tumor invasion directly into the lumen of the portal vein but simply a concentric narrowing of the vein from without. In one patient with carcinoma of the gallbladder obstruction was complete and a pinching-off of the vein occurred. Tumor infiltration into the lumen of the splenic vein took place at the splenic hilum in a case of carcinoma of the tail of the pancreas.

Primary Extrahepatic Carcinoma Arising Elsewhere. Two patients with carcinoma arising in areas other than in the upper quadrant of the abdomen but involving the liver by metastasis were examined. One was a case of melanoma, the primary having arisen in the right eye fifteen years previously. There was no extrahepatic venous deformity in this instance but equivocal evidence of intrahepatic obstruction due to extensive metastasis was present. The other patient presented with a tremendously enlarged liver. The primary carcinoma had been resected from the sigmoid colon three years previously. This patient showed definite evidence of intrahepatic obstruction. Both of these patients had diagnostic hepatograms.



5A 5B 5C

FIG. 5. (Three different cases.) A, Postmortem portogram performed at autopsy. Note constricting lesion in the hepatodistal portal vein (arrow) due to carcinoma arising in the gallbladder. (Case not included in Tables I and II.) B, percutaneous splenic portogram (film exposed at six seconds) shows constricting lesion (arrow) of the hepatodistal portal vein, due to carcinoma of head of pancreas. The diagnosis was established by biopsy specimen obtained at operation. No palpable or visible liver metastases were seen at surgery and none were demonstrated in the films. There is evidence of incomplete obstruction as indicated by collateral vein visualization, although the splenic pulp pressure was normal (90 mm. saline solution). C, carcinoma of the gallbladder. Cholecystectomy performed in May 1957 for cholecystitis and cholelithiasis. Microscopic examination revealed infiltrating anaplastic carcinoma of the gallbladder. Percutaneous splenic portogram in September 1957 shows constriction of the hepatoproximal portal vein (long arrow). Short arrow indicates defect along the medial margin of the right lobe of the liver visualized at the moment when the vasculogram and hepatogram phases are concurrent (film exposed at twelve seconds). Autopsy in December 1957 revealed lymph node metastasis involving the porta hepatis. The common duct and portal vein were completely obstructed. Infiltration into the liver at the gallbladder bed (short arrow) was found. Note that no collateral veins are visualized with only moderate narrowing of the portal vein. The splenic pressure (225 mm. saline solution) was considered to be normal.

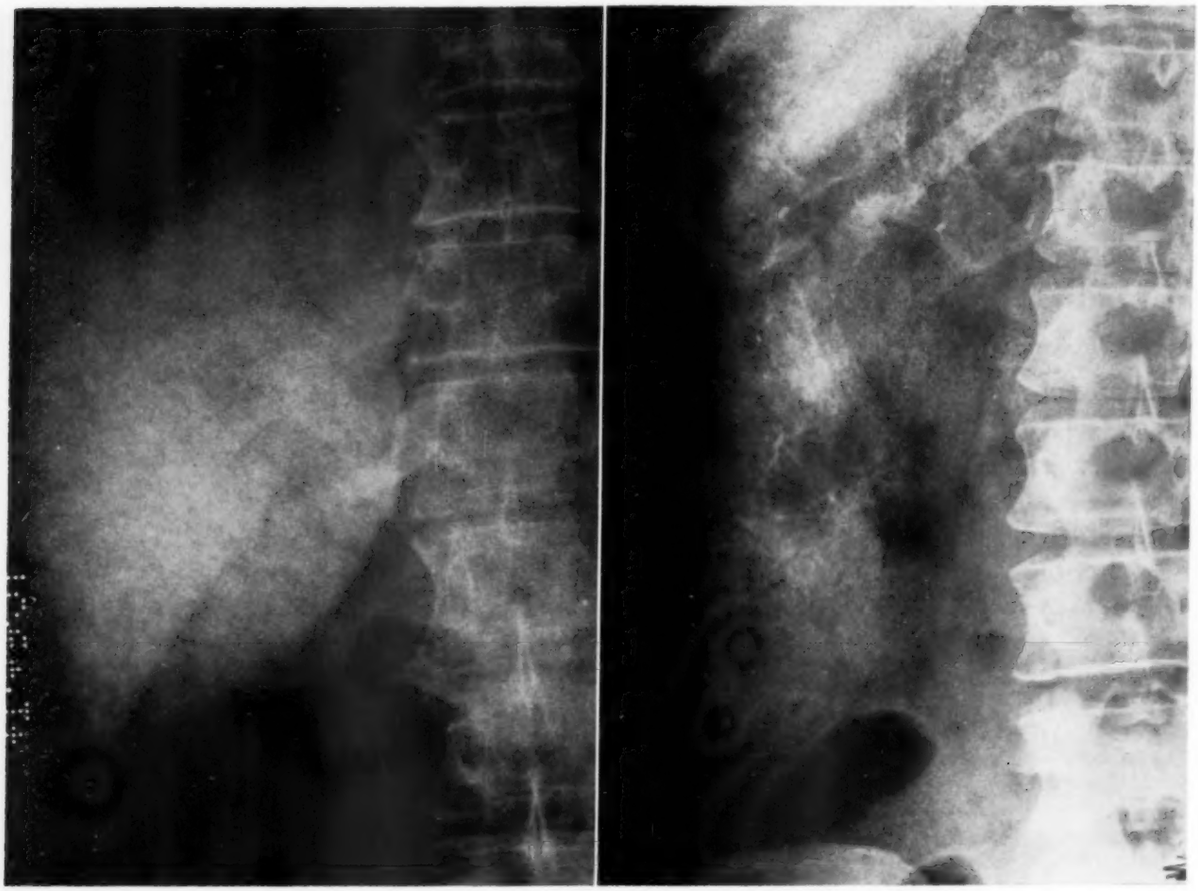
SPLENOMEGALY

It is interesting to note that of the six patients with extrahepatic primary carcinoma arising in the upper part of the abdomen in whom there was definite evidence of obstruction (collateral vein development), one had clinical and roentgenographic evidence of splenomegaly, and three others gave roentgenographic evidence of splenomegaly. (Table II.) One patient with metastatic liver carcinoma arising from a primary site outside of the upper quadrant of the abdomen (carcinoma of the sigmoid), in whom there was definite evidence of intrahepatic portal venous obstruction, had neither clinical nor roentgen evidence of splenomegaly. Of the two patients with primary carcinomas of liver, one, with equivocal evidence of obstruction (intrahepatic), had an enlarged spleen, both by palpation and by x-ray examination. The other, with complete extrahepatic obstruction, gave no evidence of splenomegaly by either method.

In summary, of the thirteen patients studied eight had definite evidence roentgenologically of portal venous obstruction as determined by collateral vein visualization. Of these eight, four had an enlarged spleen, revealed either by palpation or by roentgen examination.

DIFFERENTIAL DIAGNOSIS

Primary carcinoma of the liver is suggested roentgenologically when a single massive lesion occurs, whereas a multiplicity of lesions suggests metastasis. Should a primary carcinoma extend outside of the liver and obstruct the portal vein, a differentiation from carcinoma arising outside the liver and obstructing the vein cannot be made. The differentiation of primary carcinoma of the liver from a single inflammatory lesion such as echinococcus cyst or liver abscess also would be difficult. We have had no experience with splenoportography in the presence of inflammatory lesions of the liver. However, Nguyen Trinh Co et al. [*10*] found (in the hepatogram phase) the borders of primary liver carcinoma to be more irregular in outline than was seen with abscess. It has also been shown [*16*] that with abscess the blood vessels were not displaced or



6A 6B

FIG. 6. A, Laennec's cirrhosis. Hepatogram phase (at twenty-two seconds) shows the fairly typical generalized mottling often encountered in cirrhosis. Small defects are less well defined and more bizarre in shape than one would expect with carcinoma. Such a diffuse infiltration by metastatic carcinoma may occur but would be unusual. B, hepatogram phase in another patient with cirrhosis (at sixteen seconds). Note gross mottling compared to finer pattern in Figure 6A. The lateral margin of the right lobe of the liver is ragged in contour. Differentiation from carcinoma is very difficult in this case.

stretched out as occurs with carcinoma but were destroyed or occluded as the abscess was forming.

Metastatic disease must also be differentiated from multiple inflammatory lesions, especially if the metastases are not numerous and tend to be relatively large individually. Presumably the same differential would hold as with single lesions.

A difficult differential diagnosis might arise between cirrhosis of the liver (Figs. 6A and B) and metastatic carcinoma. In both pathologic disorders many radiolucent areas may be scattered throughout the liver in the hepatogram phase. However, it is to be noted that in cirrhosis the defects more often are irregular in shape and rather poorly defined [*14*]. The sharper definition of the defect when neoplasm is present is probably related to a relatively normal portal blood supply as well as to relatively normal liver architecture in the areas not invaded by tumor. In cirrhosis a more diffuse process involving the entire parenchyma is present, so that any opacification that occurs takes place in an abnormal parenchyma with greatly distorted and altered blood vessels. Furthermore, the vasculogram in cirrhosis, we believe, is fairly distinctive; it shows more irregularity of the caliber of larger vessels, a more generalized paucity of smaller vessels, and an over-all pattern not encountered in carcinoma. The differentiation, however, may be very difficult at times.

Interpretation of the vasculogram phase may be rendered difficult by incomplete filling of the intrahepatic portal branches. The causes of this include (1) a small delivery of opaque medium to the liver due to technical reasons, and (2)

extrahepatic or suprahepatic obstruction (e.g., a patient with hepatic vein thrombosis, the Budd-Chiari syndrome, showed this phenomenon). However, the absence of a compression-displacement effect in the vasculogram must be taken as evidence in favor of this type of failure of filling. The hepatogram phase may not help in the differential diagnosis in this situation since a hepatogram is not likely to be obtained in an area where filling of the portal branches has failed to take place. In general, it may be stated that the hepatogram tends to show the distribution of the vasculogram and, broadly speaking, the degree of vascular patency and vascular flow through an area would appear significantly to influence production of the hepatogram phase in that area.

SUMMARY AND CONCLUSIONS

The present study suggests that the roentgen method of serial percutaneous splenic portography is useful in determining the presence of, and in some measure the extent of, intrahepatic neoplasm, provided that an adequate delivery of opaque medium to the liver can be achieved. In quite limited experience, this has been possible in a majority of cases.

In the presence of hepatic neoplasm, the hepatogram phase is more informative than the vasculogram phase. In certain patients, especially those with extrahepatic obstruction, it is important to obtain late as well as early exposures, even up to sixty seconds after the start of the injection. The greater part of the medium tends to pass into the right lobe of liver under ordinary circumstances; possibly further improvement in technic will correct this deficiency. At the present writing it would appear that a positive diagnosis of carcinoma in liver is more meaningful than a negative one.

It is our opinion that the method of splenic portography is much less useful in detecting the presence of extrahepatic neoplasm in the upper quadrants of the abdomen. It may prove to be of some value, however, in determining portal or splenic vein extension and thus the operability of the lesion. A strategically situated neoplasm may of course, produce a deformity of the extrahepatic system early in the course of the disease, but our experience suggests that ordinarily this does not occur. A final opinion, however, is not justified by this material and must await the study of a larger series.

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Clinical and Laboratory Studies of Plasma Thromboplastin Antecedent Deficiency (PTA)*

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UNTIL recently the term hemophilia denoted an hereditary disorder of blood coagulation appearing clinically in males and transmitted by females apparently unaffected by this disease. However, Pavlovsky [*1*], mixing the plasmas of two patients with hemophilia showed mutual correction of their coagulation defects, thus demonstrating that hemophilia was not a single disease. Refinements of technic, such as the thromboplastin generation test of Biggs and McFarlane [*2*], subsequently have shown that the original hemophilia actually consists of at least five distinct coagulation defects.

One of the defects of plasma thromboplastin generation, plasma thromboplastin antecedent (PTA), described originally by Rosenthal, Dreskin and Rosenthal [*3–5*], was found not to be sex-linked in its passage and therefore present not only in males but transmitted as an autosomal dominant independent of sex linkage.

The disease as originally described by Rosenthal and co-workers was that of a mild, familial coagulation disease, occurring in males and females, and exhibiting bleeding principally after trauma or operations. Coagulation times were prolonged; prothrombin consumption was abnormal, correction being accomplished by the addition of normal serum, normal plasma, $BaSO_4$-absorbed normal serum, and mixtures of serum from the patient plus normal serum. These observations have also been confirmed using the thromboplastin generation test. The prothrombin times were normal. It was also noted that PTA activity increased when serum or plasma was kept at room temperature or in the frozen state; this caused some difficulty in reproducing results when samples were sent to other laboratories. Soulier, Wartelle and Mensche [*6*] commented in this connection on the relationship between the Hageman and PTA factors. Their conclusions were that the Hageman factor is first activated by glass and subsequently activates the PTA factor in the presence of calcium. They therefore place PTA and Hageman factors in the very initial states of coagulation.

The present investigation was prompted by an opportunity to study several members (two generations) in a family with PTA deficiency. In addition, we have gathered data concerning five other patients who were not related with this deficiency seen by us over the past two years.

METHODS

The patients in question were studied by means of the following tests: (1) Lee and White coagulation time [*7*]; (2) plasma recalcification coagulation time; (3) prothrombin time, the one-stage method of Quick with control time of twelve seconds [*8*]; (4) the thromboplastin generation tests as outlined by Biggs and MacFarlane with substitutions in this system as described [*2*]; (5) thromboelastography, utilizing the Haemoscope;† and (6) partial thromboplastin time [*9*].

CASE HISTORIES

The family previously mentioned first came to our attention when one member (W. B.) was seen with menorrhagia. A second patient was seen recently for persistent, severe epistaxis. Careful evaluation of seven additional members of the family was carried out.

CASE 1. W. B., a seventeen year old girl, was admitted to Ohio State University Hospital on January 23, 1959, for profuse menorrhagia of twenty days' duration. No other symptoms were noted. The onset of menses had been at the age of thirteen with no previous irregularity or excessive flow. She had had occasional epistaxis in the past, the last episode taking place seven years previously. Her hemoglobin on admission was 7.8 gm. per cent. The remainder of the blood count was as follows: white blood cells 11,600 per cu. mm., red blood cells 3,150,000 per cu. mm., reticulocytes 3.4 per cent, platelets 875,700 per cu.

† Haemoscope from the Haemoscope Corporation, Albertson, New York.

* From the College of Medicine, The Ohio State University, Columbus, Ohio. This investigation was supported in part by U.S. Public Health Service Research Grant C-2472 (Hematology).

mm. The results of coagulation studies were as indicated in Table 1. The impression was that of PTA deficiency and treatment consisted of the administration of whole stored blood. On January 29, 1959, she was discharged improved, with no further bleeding, and has done well since.

CASE II. S. B., JR., a thirteen year old boy, was admitted to Ohio State University Hospital for severe epistaxis of one day's duration. He gave a history of severe recurrent epistaxis since the age of two years, requiring occasional hospitalization for transfusion. The last severe epistaxis had taken place one year previously. On admission to the hospital a unit of blood was being infused. Hemoglobin was 6.9 gm. per cent, and white blood cells 11,750 per cu. mm. Two additional units of fresh blood were given. Initial coagulation studies were invalid because of the blood already administered, but later studies showed the characteristics of PTA deficiency. (Table 1.) He was discharged asymptomatic May 17, 1959. His hemoglobin at the time of discharge was 11.5 gm. per cent.

CASE III. X, a female child, died of severe epistaxis at fourteen months of age. She was not available for study.

CASE IV. S. H. B., a fifteen year old girl, gave no history of bleeding tendency. Her menses were normal.

CASE V. S. K. B., a twelve year old girl, gave a vague history of epistaxis with trauma but with no other bleeding tendency.

CASE VI. K. B., a five year old girl, had no bleeding tendency.

CASES VII and VIII. P. B., a three year old male infant, and B. B., a two year old male infant, likewise had no history of abnormal bleeding.

CASE IX. R. B. (mother of the eight children, Cases I to VIII) had no history of abnormal bleeding. There had been no difficulty at the time of menses, trauma, childbirth or operation.

CASE X. S. B., Sr. (father of the eight children, Cases I to VIII) had no history of abnormal bleeding. One year previously he had had a traumatic subdural hematoma requiring multiple trephinings.

Comments: As can be seen from Figure 1 there are six persons with a history of bleeding in this family over the past two generations. The lineage apparently follows the ancestry of the mother (R. B.), and males and females have been affected with equal severity and incidence. Some exhibit epistaxis, menorrhagia, or post-traumatic bleeding of moderate severity, one (a fourteen month old infant) died of uncon-

TABLE 1

COAGULATION STUDIES OF PTA DEFICIENCY ON FAMILY B AND FIVE UNRELATED PATIENTS

Coagulation Tests	Normal	Family B									Unrelated Cases				
		W. B. (Case I)	S. B. Jr. (Case II)	S. H. B. (Case IV)	S. K. B. (Case V)	K. B. (Case VI)	P. B. (Case VII)	B. B. (Case VIII)	R. B. (Case IX)	S. B. Sr. (Case X)	M. F. (Case 1)	B. F. (Case 2)	D. R. (Case 3)	D. S. (Case 4)	W. F. (Case 5)
Coagulation times															
Lee-White	8–11 min.	32 min.	19 min.	29 min.	29 min.	14 min.	29 min.	21 min.	16 min.	9 min.	20 min.	15 min.	18 min.	24 min.	14 min.
Recalcified plasma	120 sec.	245 sec.	170 sec.	135 sec.	190 sec.	120 sec.	225 sec.	205 sec.	120 sec.	120 sec.	...	...	...	...	...
Thromboelastograph															
r	7–26 mm.	33	30	22	19	21	21	23	33	...	22	30	...	...	...
k	3–15 mm.	13	10	6	9	4	12	10	14	...	6	8	...	...	...
ma	40–70 mm.	60	64	60	60	62	59	61	61	...	68	62	...	...	...
Quick one-stage prothrombin time	12 sec.	12.4 sec.	13.0 sec.	11.8 sec.	12 sec.	12 sec.	12 sec.	12.7 sec.	12.7 sec.	12.8 sec.	13.2 sec.	12.2 sec.	12 sec.	12.4 sec.	13.4 sec.
Thromboplastin generation test†															
Patient system	...	Abnormal	Abnormal	Normal*	Abnormal	Abnormal	Abnormal	Abnormal	Abnormal*	Normal	Abnormal	Abnormal	Abnormal	Abnormal	Abnormal
Normal serum 1:5 substituted	...	Corrected	Corrected	...	Corrected	Corrected	Corrected	Corrected	Corrected	...	Corrected	Corrected	Corrected	Corrected	Corrected
Normal $Al(OH)_3$ absorbed plasma substituted	...	Corrected	Corrected	...	Corrected	Corrected	Corrected	Corrected	Corrected	...	Corrected	Corrected	Corrected	Corrected	Corrected
0.15 ml. $BaSO_4$ serum 1:5, plus 0.15 ml. patient serum 1:5, substitute for patient serum	...	Corrected	Corrected	...	Corrected	Corrected	Corrected	Corrected	Corrected	...	...	...	Corrected	Corrected	Corrected
0.15 ml. normal serum 1:5, plus 0.15 ml. patient serum 1:5, substitute for patient serum	...	Corrected	Corrected	...	Corrected	Corrected	Corrected	Corrected	Corrected	...	...	...	Corrected	Corrected	Corrected
Partial thromboplastin test	80–90 sec.	...	152 sec.	84 sec.	...	81 sec.	...	...	...	...	97 sec.	147 sec.	...	...	...

* See text.
† Normal platelets substituted in all generations showed no corrections of defect.

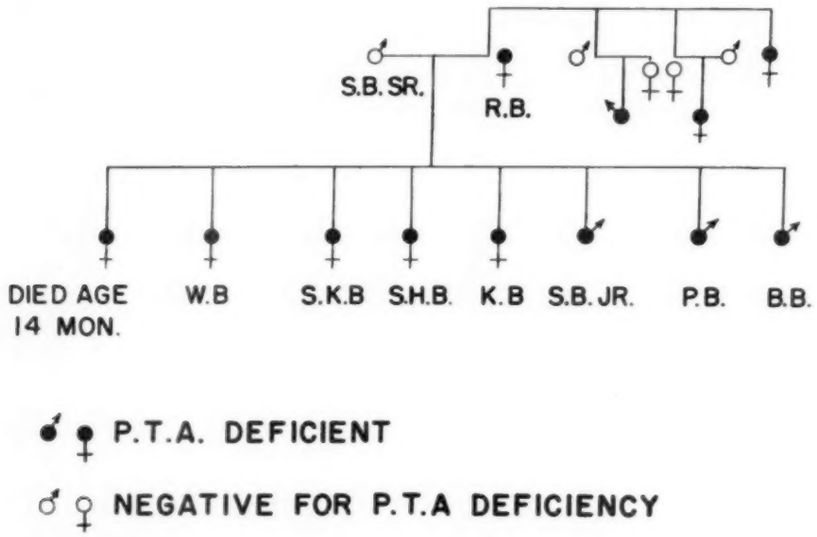


FIG. 1. Family tree of family B. The parents, S. B., Sr. and R. B., and seven siblings were studied by coagulation tests. Other relatives were not available for testing.

trolled epistaxis, another (S. B. Jr.) had a hemoglobin of 6.9 gm. per cent after bleeding in less than twenty-four hours after trauma to the nose.

The coagulation data (Table 1) show widespread involvement of all seven siblings by the PTA defect. Coagulation times were prolonged in all and the thromboplastin generation test revealed a corresponding defect in all but one case. This defect was corrected by normal serum, $Al(OH)_3$ absorbed plasma, $BaSO_4$-absorbed serum, or a mixture of normal serum and the patient's serum. In the aforementioned subject (S. H. B.) the thromboplastin generation test revealed no abnormalities; however, she did not correct the deficiency in one of her siblings (S. B. Jr.), thus demonstrating involvement by the disease. R. B. (the mother) showed a moderately prolonged coagulation time with an abnormal thromboplastin generation time which was corrected as noted. However, she exhibited no clinical bleeding. The father (S. B. Sr.) was entirely normal in regard to his coagulation tests. We conclude, therefore, that the mother (R. B.) is the means of transmission of the defect to the seven children. This is corroborated by the genetic background of the family, which reveals three persons with clinical bleeding, all related to R. B.

The prothrombin times were uniformly normal, the plasma recalcification times were highly variable, from normal to moderately prolonged. Thromboelastography did not add significantly to the study.

It thus appears that the deficiency (PTA) is transmitted as an autosomal dominant with in-

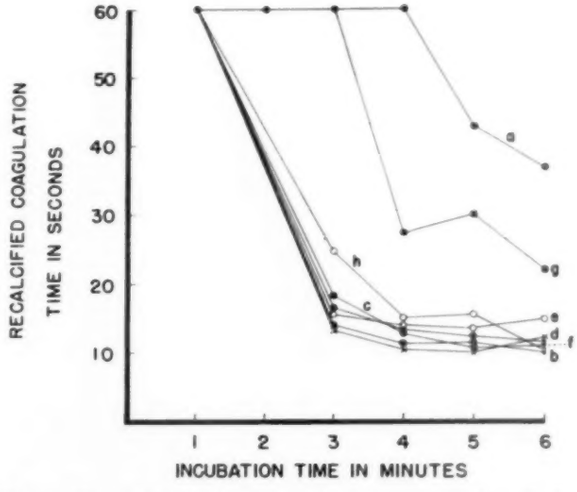


FIG. 2. Thromboplastin generation Tests on patient P. B. (a) Patient's system; (b) normal serum 1:5 substituted for patient's serum; (c) normal plasma absorbed with $Al(OH)_3$ substituted for patient's plasma; (d) 0.15 ml. normal serum absorbed with $BaSO_4$ 1:5 plus 0.15 ml. patient serum substituted for patient serum 1:5; (e) 0.15 ml. normal serum 1:20 plus 0.15 ml. patient serum 1:5-substituted for patient serum; (f) plasma from PTC deficient patient substituted for patient plasma; (g) patient's plasma plus serum from unrelated PTA deficient patient (M. F.) showing lack of correction; (h) patient's serum plus plasma from AHG deficient patient; patient's platelets used in all generation tests.

complete penetrance and variable expressivity. Our incidence is somewhat higher than reported by other authors, but is consistent with the heredity pattern postulated.

Of interest is the fact that, regardless of the severity of the defect in this family group, all were easily controlled by the administration of fresh or stored blood. In one patient (S. B. Jr.) the coagulation defect was corrected by the administration of 250 cc. of stored blood and all bleeding stopped after two units more were given.

Five more examples of PTA deficiency have been found in our laboratory over the past two years. The same methods were employed as in the previous cases. (Table 1.)

CASE I. M. F., a forty-two year old white woman, had a history of marked hematoma of the left side of the face after a tooth extraction. Her past history showed numerous episodes of bleeding at times of trauma or surgery. The menses had been normal. Her family history revealed several bleeders on her maternal side, her mother died of profuse hemorrhage at the time of a delivery. The blood count was normal with adequate platelets and hemoglobin.

CASE II. B. F., a thirty-three year old white woman, had a history of menorrhagia of nine years' duration, and excessive bleeding from minor cuts. She had undergone surgery without difficulty on one occasion, but had severe bleeding on another and also at the time of tooth extractions. One brother gave a history of severe epistaxis.

CASE III. D. R., a nineteen year old white girl, was seen for hemorrhage after tooth extractions. Examination and complete blood count were within normal limits. Her family history showed three "bleeders" on the maternal side, one having died from traumatic bleeding of an extremity.

CASE IV. D. S. was a six year old white boy with no clinical bleeding. Examination and complete blood count were within normal limits. Coagulation studies revealed a deficiency of PTA. It is of interest that he underwent surgery for an inguinal herniorrhaphy in the past without difficulty.

CASE V. W. F., an eight year old white girl, presented with a history of frequent spontaneous and traumatic epistaxis. It had been noted that she bruised easily. She had several teeth extracted for infection without sequelae.

COMMENTS

With the development of the modern concept of plasma thromboplastin, the original hemophilia has been subdivided into several groups, each lacking a specific thromboplastin factor. Classic hemophilia lacks antihemophiliac globulin (AHG), which being quite labile can be supplied only by the administration of fresh blood or fresh frozen plasma. Christmas disease lacks plasma thromboplastin component (PTC). This is a stable factor and can be given as stored blood or plasma. The Hageman factor is essential for glass activation, but a deficiency of it does not cause a bleeding tendency. The Stuart factor has a dual role in the formation of plasma thromboplastin and prothrombin conversion to thrombin, and thus can be identified by coagulation studies. PTA is the remaining factor of significance. It has been shown to be active in plasma and serum, and to be present after $BaSO_4$ absorption, thus delineating it from both AHG and PTC.

As initially described, PTA deficiency was thought to be the rarest and the mildest of the hemophilioid states. Frick [*10*] stated in 1954 that of fifty-five cases of hemophilia restudied, four had PTA deficiency, an incidence of only 7.3 per cent. Ratnoff [*11*] stated in 1958 that of 105 families reported by three groups, only six were deficient in PTA. He adds, however, that difficulties in performing coagulation studies may have been a factor in this low incidence, many being considered to have PTC deficiency.

It is obvious from the preceding case reports that this entity cannot be considered uniformly mild, but that it can on occasion be as lethal as any other coagulation disorder, and should be treated as vigorously as classic hemophilia or Christmas disease. We would agree with the postulated mode of inheritance as an autosomal dominant, but emphasize the variable expressivity and incomplete penetrance.

The therapeutic importance of distinguishing AHG, PTC, PTA and Hageman defects lies in the type of material needed to correct the defect clinically. The thromboplastin generation test with the various admixture experiments gives clues as to what is actually required to stop bleeding and correct the coagulation time. Thus hemophilia requires fresh blood or plasma, while PTC and PTA deficiencies can be corrected by stored blood or plasma. This could be of critical importance if the available supply of fresh material is low.

SUMMARY

Fourteen patients with PTA deficiency are reviewed, including a family with six bleeders

in the past two generations. Data are presented which show that the bleeding tendency in this disorder is often mild, as hitherto emphasized, but may also be of moderate or severe degree. Heredity appears to be by an autosomal dominant gene with variable expressivity and incomplete penetrance.

Acknowledgment: We wish to acknowledge the technical assistance of Miss Delma Moore, R.N., M.T.

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Further Observations on Leukoagglutinin Transfusion Reactions*

With Special Reference to Leukoagglutinin Transfusion Reactions in Women

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THE leukoagglutinin transfusion reaction has been separated in recent years from other types of febrile transfusion reactions [*1–5*]. This newly defined reaction has been found to follow the transfusion into patients with leukoagglutinins of leukocyte-incompatible blood [*4,6*]. Preliminary surveys indicated that leukoagglutinins occurred especially frequently in the serums of patients with febrile transfusion reactions [*3,7*]. These reactions could be prevented by the removal of buffy coat from whole blood [*1–3*]. In the initial studies on this type of reaction, one of the particular features noted was the relatively large number of transfusions necessary before leukoagglutinins and febrile reactions developed [*3*]. In the majority of patients having such reactions a total of ten to twenty units of blood had been administered over a period of months. As information on leukoagglutinin transfusion reactions accumulated, some exceptions to this requirement of a large number of transfusions were observed. Payne and Rolfs [*8*] described two women, one who had a febrile reaction after her first transfusion and the other after her second. The leukoagglutinins of these two women were deduced to be the result of stimulation by fetal leukocytes. Both Killmann [*9*] and Zucker et al. [*10*], who observed febrile transfusion reactions and leukoagglutinins in parous women after very few transfusions, did not comment on the relation of the leukoagglutinin to prior fetal stimulation. However, in a later publication Killmann [*11*] noted that "the role of pregnancy as a cause of leukocyte agglutinins remains to be assessed."

The objective of the current study is to present more extensive experience on the nature and prevention of leukoagglutinin transfusion reactions in men and women. It will be shown that the majority of serums from 221 patients with febrile transfusion reactions contained leukoagglutinins, that women comprised a relatively large proportion of the persons with leukoagglutinin transfusion reactions, and that this occurred in many women after fewer transfusions than in men. This difference in the number of transfusions required to induce reaction in women will be related to prior stimulation of fetal leukocytes.

METHODS

Test for Isoleukoagglutinins. The details of our methods have been reported in previous publications [*3,8,12*]. Briefly, in the survey for the presence of leukoagglutinins, heat-inactivated serums are tested for their capacity to agglutinate any two or more members of a panel of ten leukocyte donors of red cell group O. All leukocytes are used on the day of collection. To establish that leukoagglutinins in women may have arisen from stimulation by fetal leukocytes, leukocytes are also obtained from the husband and/or the children of the patient. When the red cell groups within a family are different, the serums are appropriately absorbed to prevent false positive reactions which may result from the action of red cell isoagglutinins on residual red cells in the white cell suspension. Serums of the patients with "immune" red cell agglutinins are tested with leukocyte suspensions in which the red cell residuum lacks the complicating antigen, e.g., a serum with anti-D is tested with leukocytes from Rh-negative donors.

Sources of Serums. All the serums were referred to this laboratory because the patients had suffered either a febrile or an allergic transfusion reaction.

* From the Department of Medicine, Stanford University School of Medicine, Palo Alto, California. This study was supported by research grant H-3365, National Institutes of Health, U. S. Public Health Service.

TABLE I
INCIDENCE OF RED AND WHITE CELL AGGLUTININS IN THE SERUMS OF 221 PATIENTS WITH FEBRILE TRANSFUSION REACTIONS

Condition of Patient	No. of Patients	Proportions
With leuko-agglutinins	147	147/221 = 67 per cent
With red cell agglutinins	18	18/221 = 8 per cent

These subjects were largely from the San Francisco area.

Preparation of "Leukocyte-Poor" Blood for Transfusion. Three methods for the preparation of "leukocyte-poor" blood were utilized. The majority of the patients received fresh blood collected into bottles containing acid-citrate-dextrose solution. The buffy coat was removed by skimming after centrifugation, as described in an earlier publication [*3*]. As the demand for this type of preparation increased a simpler method was instituted. Blood was collected in plastic bags for centrifugation in the cold (5°c.). The plasma and buffy coat layer were expressed with a Fenwal plasma extractor. Leukocyte-poor units prepared by the dextran sedimentation technic devised by Chaplin, Brittingham and Cassell [*13*] were also employed in the treatment of three patients.

RESULTS

Febrile Transfusion Reactions. Incidence of red and white cell agglutinins: In order to obtain additional information on the leukoagglutinin transfusion reaction, the serums of 221 patients with febrile transfusion reactions were examined for antibodies to leukocytes and erythrocytes. The serums from 147, or 67 per cent, of the patients with febrile transfusion reactions were found to have leukoagglutinins. The incidence of antibodies to leukocytes was high as compared to that for erythrocytes. Only 18, or 8 per cent, of the serums contained red cell antibodies. (Table I.) These included cold agglutinins, Rh antibodies and autoagglutinins. Of these eighteen serums with red cell agglutinins, ten also possessed leukoagglutinins.

Distribution of leukoagglutinins: The distribution of leukoagglutinins among men, women and children with febrile transfusion reactions is presented in Table II. There were more women than men with febrile transfusion reactions. The proportion of women with leukoagglutinins was greater than that for men. Using the chi square test, the difference between the proportions of 90/125 for women and 47/82 for men was statistically significant at the 5 per cent level.

TABLE II
DISTRIBUTION OF LEUKOAGGLUTININS AMONG MEN, WOMEN AND CHILDREN WITH FEBRILE TRANSFUSION REACTIONS

Patients	Total No. of Patients	Patients with Leuko-agglutinins	Proportions
Adult women	125	90	90/125 = 72%
Adult men	82	47	47/82 = 57%
Children	14	10	10/14 = 70%
Total	221	147	

Relation of leukoagglutinin distribution to number of transfusions: A tabulation of the number or series of transfusions received by each patient was prepared, considering only those patients with leukoagglutinins. (Table III and Figure 1.) All transfusions administered within a five-day period are considered as a series acting as a single stimulus. Thus a patient with a one-transfusion stimulus may actually have received one or several units of blood. The key observation here was that about a half, or forty-four of ninety women, had a reaction to the first or second

TABLE III
RELATION OF NUMBERS OF MEN, WOMEN AND CHILDREN IN WHOM LEUKOAGGLUTININS AND FEBRILE REACTIONS TO TRANSFUSION DEVELOPED TO THE NUMBER OF TRANSFUSION STIMULI RECEIVED*

No. of Transfusion Stimuli	No. of Subjects		
	Men	Women	Children
1	0	23	0
2	0	21	0
3	2	9	0
4	2	5	0
5	1	2	0
6	2	4	0
7	5	2	0
8	3	1	0
9	1	0	0
>10	31	23	10
Total	47	90	10

* All transfusions administered within a five-day period are considered to act as a single antigenic stimulus.

transfusion stimulus. This was in marked contrast to the forty-seven men with leukoagglutinins, none of whom showed evidence of reaction to so few transfusions. With regard to the larger number of transfusions, there were sixty-four patients who had received ten or more transfusions before a reaction was reported; these included all ten of the children, two-thirds of the men, and a quarter of the women. Of these sixty-four patients there were nine who had received between ten and nineteen transfusions, and thirty-nine who had received more than twenty transfusions. Of the latter group twenty-one patients had had more than fifty transfusions. At all these increased levels of transfusions, appreciable differences between the proportions of men, women and children did not appear.

Explanation of leukoagglutinin transfusion reactions in women receiving one or two transfusion stimuli: In searching for an explanation of why women had leukoagglutinin transfusion reactions after very few transfusion stimuli, it seemed plausible to consider that leukoagglutinins might have developed during pregnancy. With this in mind, the obstetrical histories of these women were reviewed. (Table IV.) Of the twenty-three women who reacted to their first transfusion stimulus, twenty women had had one or more pregnancies; the records on three of the women did not contain information regarding gravidity. Of the twenty-one women who reacted to their second transfusion stimulus, eighteen had a history of past pregnancy; pregnancy data were not available on two women. One woman was reported not to have borne children. These findings are consistent with the idea that stimulation by fetal leukocytes may have been responsible for the reactions in women after so few transfusions.

Another parameter of the problem of the origin of their leukoagglutinins was explored. Could the possibility exist that in the group of women who reacted to their first transfusion stimulus, but in whom no leukoagglutinins could be detected, a greater proportion would be nonparous persons? A larger proportion of nonparous women would be expected if fetal leukocytes were the stimulus for leukoagglutinin formation in the parous women. This in fact turned out to be the situation since six of eighteen, or 33 per cent, of the women without leukoagglutinins were not parous whereas only one of thirty-nine, or 2.6 per cent, was not parous among the women with leukoagglutinins.

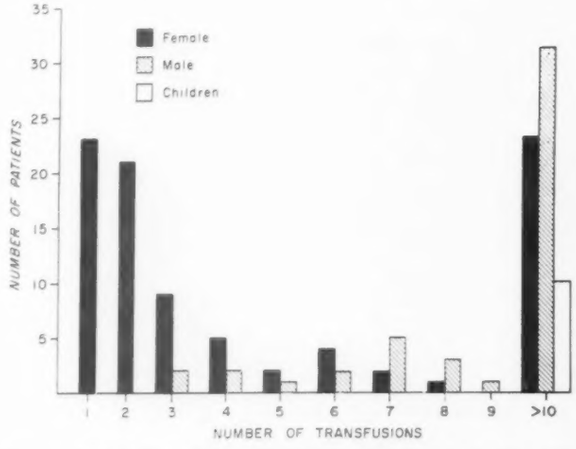


FIG. 1. Relation of numbers of men, women and children in whom leukoagglutinin transfusion reactions developed to numbers of transfusion stimuli received.

(Table V.) The foregoing data on pregnancy added to the known occurrence of leukoagglutinins in pregnant women after stimulation by fetal leukocytes [*8*] would suggest that the women reported on herein who reacted to their first or second transfusion stimulus had also been stimulated by fetal leukocytes during pregnancy. The coincidence of past pregnancy, leukoagglutinins and a febrile transfusion reaction after few transfusions does not, however, by their association establish a cause and effect relationship.

More decisive evidence to support the proposal that the women with leukoagglutinins who reacted to their first transfusion had been previously stimulated by fetal leukocytes would be the demonstration of agglutination by the maternal serums of the leukocytes of the husband or child. This approach is based on studies which had shown that leukocyte antigens appeared to be inherited in a manner similar to that for red cell antigens [*8,14,15*]. The results of agglutination tests with the serum of patient No. 2 are shown in the pedigree of Figure 2. This woman had a marked febrile reaction on her first transfusion in 1958. Both the leukocytes of her two children and her spouse were strongly agglutinated by her serum. The last stimulation prior to transfusion would appear to be from her youngest child born twelve years ago. Both children possessed leukocyte antigens absent in the mother. Nine families in which the mother had reacted to her first transfusion were studied. (Table VI.) The husband and children were tested in five families, the husband only in two families, and the children only in two families.

TABLE IV

DATA ON WOMEN IN WHOM BOTH LEUKOAGGLUTININS AND FEBRILE TRANSFUSION REACTIONS WERE EXHIBITED AFTER THEIR FIRST AND SECOND TRANSFUSION STIMULI

No. of Patient	No. of Pregnancies	Time Since Last		Transfusions	Diagnosis and Remarks
		Pregnancy	Transfusion		
1	7	9 yr.†	None	1	Chronic lymphatic leukemia, repeated transfusion reactions
2	2	12 yr.	None	1	Duodenal ulcer
3	8	24 yr.	None	1(2)‡	Carcinoma of the cervix
4	4	Pregnant	None	1	Pregnancy, transfusions during cesarean
5	3	29 yr.	None	1(3)	Chronic pyelonephritis
6	3	15 yr.	None	1	Rectal bleeding
7	1	12 yr.	None	1(5)	Hysterectomy
8	3	15 yr.	None	1(2)	Carcinoma of the breast
9	4	5 yr.	None	1(3)	Chronic granulocytic leukemia
10	1	39 yr.	None	1	Thrombosis
11	2	2 yr.	None	1	Polycystic kidney
12	2	8 yr.	None	1(2)	Bleeding cervix
13	8	Pregnant	None	1	Incomplete abortion during first trimester
14	1	Pregnant	None	1(4)	Pregnancy, transfusion at delivery
15	5	Pregnant	None	1(2)	Pregnancy, third trimester
16	3	Pregnant	None	1	Post partum bleeding
17	NA*	24 yr.	None	1(4)	Chronic pyelonephritis and pernicious anemia, another reaction on second series of transfusions
18	9	3 yr.	None	1(3)	Common duct exploration
19	2	3 yr.	None	1(8)	Anemia of blood loss
20	3	3 yr.	None	1	Lymphoma, another reaction with second unit given six months later
21	NA	7 yr.	None	1	Acquired hemolytic anemia
22	1	NA	None	1(2)	Acute myelogenous leukemia
23	NA	NA	None	1(2)	Disseminated lupus erythematosus
24	2	13 yr.	1 wk.	2(5)	Carcinoma of the cervix
25	6	5 yr.	3 yr.	2	Carcinoma of the ovary
26	NA	NA	5 yr.	2	Dilatation and curettage
27	4	Pregnant	5 yr.	2(3)	Pregnancy, transfusion with cesarean
28	5	Pregnant	18 mo.	2(4)	Dilatation and curettage
29	3	NA	2 mo.	2(6)	Acute glomerular nephritis, repeated transfusion reactions
30	5	Pregnant	1 yr.	2(4)	Spontaneous abortion during second trimester
31	2	3 yr.	3 yr.	2(4)	Fractured rib
32	3	NA	NA	2	Vaginal repair
33	3	3 yr.	12 days	2(5)	Chronic renal disease
34	0	None	2 mo.	2(7)	Carcinoma of the breast
35	5	3 yr.	4 yr.	2	Vaginal hemorrhage
36	2	NA	NA	2	Hemorrhoids, anemia and cirrhosis
37	3	33 yr.	2 wk.	2(10)	Carcinoma of the pancreas
38	5	35 yr.	NA	2(5)	Carcinoma of the colon
39	3	20 yr.	1 yr.	2(5)	Cirrhosis
40	NA	NA	1 wk.	2(4)	Acquired hemolytic anemia
41	7	NA	4 yr.	2	Mitral stenosis
42	3	NA	1 wk.	2(6)	Carcinoma of the cervix
43	1	24 yr.	17 days	2(4)	Chronic myelogenous leukemia; another reaction at fourth series given three weeks later
44	5	23 yr.	4 mo.	2(10)	Gastrointestinal bleeding

* NA indicates data not available.

† Estimated, assuming age of patient at last pregnancy was fifty years.

‡ Number without parentheses indicates transfusion stimuli; number inside parentheses indicates total units of blood.

TABLE V
RELATION OF PARITY TO PRESENCE OF LEUKOAGGLUTININS IN WOMEN WITH FEBRILE TRANSFUSION REACTIONS TO FIRST OR SECOND TRANSFUSION STIMULI

Condition of Patient	No. of Women			
	Parous	Nonparous	Total	Proportions
With leukoagglutinins	38	1	39	1/39 = 2.6%
Without leukoagglutinins	12	6	18	6/18 = 33.0%

In eight of nine cases, the maternal serum agglutinated the leukocytes of one or more members of the family. The results were negative in one family. A possible explanation for the negative results follows. In this woman the febrile transfusion reaction occurred three years after the patient's last pregnancy. The patient reacted to the fourth unit in a series of eight transfusions administered over a one-week period. The original leukoagglutinating sample of serum was drawn two months after the reaction. The negative sample of serum used in the family study was obtained five months after the positive one, making a total of seven months from the time of reaction. The quantity of leukoagglutinin may have declined below detectable levels when the family study was undertaken. Such a subsidence of leukoagglutinin was observed in three of thirty-seven

TABLE VI
RELATION OF LEUKOCYTES OF FAMILY MEMBERS TO LEUKOAGGLUTININS IN WOMEN WITH TRANSFUSION REACTIONS TO FIRST TRANSFUSION STIMULUS*

No. of Women Patients Tested	Leukocytes of	
	Spouse	Child
4	+	+
1	−	−
2	+	Not tested
2	Not tested	+

NOTE: Maternal serums were tested for agglutination of leukocytes of respective husband and/or child.

* + indicates positive agglutination test; − indicates a negative agglutination test.

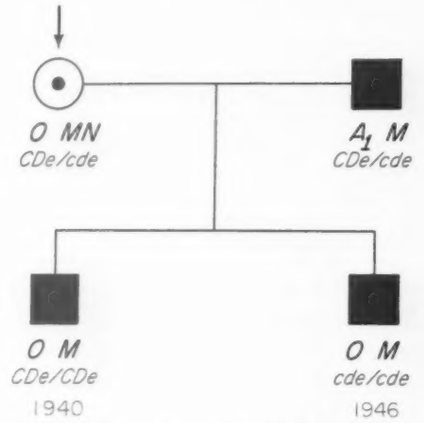


FIG. 2. Case 2. Propositus with febrile reaction to first transfusion. Family study with serum of a woman patient who suffered a leukoagglutinin transfusion reaction on her first transfusion. The pedigree illustrates the presence of a factor in the leukocytes of two children and the husband which could have stimulated the patient to produce leukoagglutinins during pregnancy. Black = leukocyte factor present; dot = leukocyte factor absent; dates = birth dates.

women six weeks postpartum, with more below detectable levels after longer periods of time. Dausset [*16*] showed that leukoagglutinins may disappear in a multitransfused patient. In regard to the women who reacted to their second transfusion stimulus, only one family was tested to indicate the likelihood of stimulation by fetal leukocytes. This patient's serum agglutinated the leukocytes of her husband, thus suggesting the same mechanism for the formation of antibodies as in the women with a reaction after their first transfusion stimulus.

Allergic Transfusion Reactions. Data on fifty-seven patients with allergic reactions, usually urticarial, are provided in Tables VII and VIII. There were twenty-three women, thirty-one men, and three children. Twelve persons, or

TABLE VII
INCIDENCE AND DISTRIBUTION OF RED AND WHITE CELL AGGLUTININS IN THE SERUMS OF FIFTY-SEVEN PATIENTS WITH ALLERGIC (USUALLY URTICARIA) TRANSFUSION REACTIONS

Condition of Patient	No. of Patients	Proportions
With leukoagglutinins	12	12/57 = 21%
Adult women	6	
Adult men	5	
Children	1	
With red cell agglutinins	2	2/57 = 3.5%

TABLE VIII

COMPARISON OF THE NUMBER OF PERSONS IN WHOM LEUKOAGGLUTININS AND ALLERGIC REACTIONS DEVELOPED TO THE NUMBER OF TRANSFUSION STIMULI RECEIVED

No. of Transfusion Stimuli	No. of Patients		Total
	With Leukoagglutinins	Without Leukoagglutinins	
1–2	3	20	23
3–9	6	18	24
>10	3	7	10
Total	12	45	57

21 per cent, of the patients had leukoagglutinins in their serums as compared to the much larger proportion of 67 per cent in the series of febrile reactions. The distribution of leukoagglutinins was about equal between men and women in this small group. The three persons who possessed leukoagglutinins after the first or second transfusion stimuli were parous women, the other nine persons were multitransfused.

Prevention of Leukoagglutinin Transfusion Reactions. Forty patients with leukoagglutinin transfusion reactions were treated with leukocyte-poor blood. The period of treatment and the number of units administered were variable, depending on the nature of the disease. Many of the patients were in the terminal phase of leukemia, receiving a few units during a relatively short period of time with prevention of reactions. Long term treatment with multiple transfusions was also successful in preventing the recurrence of any kind of reaction in four patients. One patient with thalassemia major received a total of 23 units (an average of two units every two months) during twenty-one months. Three other patients with aplastic anemia received respectively 18 units at irregular intervals during nine months, 54 units (an average of three each month until the terminal phase) during eleven months, and 18 units (an average of two each month) during eight months. The number of units used for these patients was more than customary because of the loss of red cell mass during preparation of leukocyte-poor blood. Sensitization to red cell antigens developed in one patient during this period of treatment. The only failures to prevent reaction with this type of preparation occurred in the initial trials when the reduction of leukocyte numbers was too small. A leukocyte count of 750 per cu. mm. of the red cell mass was sufficiently low to prevent reaction in all the patients tested. A total of 530 units of leukocyte-poor blood was prepared for these forty patients during a period of three years. A demand for this type of unit averaged 80 units per year for the first two years, and increased to 318 leukocyte-poor units this past year. Units prepared by the dextran sedimentation technic were used in the treatment of three patients. The number of trials was insufficient for evaluation of this method. No attempt was made to find blood containing compatible leukocytes, for in multitransfused patients the likelihood of finding such a unit is small. The leukoagglutinins of these patients generally react with a great variety of test leukocytes because the majority of referred patients were stimulated by either many or widely distributed leukocyte antigens.

COMMENTS

The extensive use of transfusions in the therapy of patients has produced an ever increasing variety of sensitizations to the constituents of blood. The most recently described sensitization develops from exposure to incompatible leukocytes which induce the formation of leukoagglutinins, and on subsequent transfusions of leukoagglutinin reactions. These reactions appear during or within two hours of transfusion. They usually begin with a chill and are characterized by significant fever with elevation of temperature of more than 1°C. More severe manifestations, such as a fall in blood pressure, nausea, vomiting and chest pain, may occur. It was the aim of this investigation to seek new information by the detailed study of a larger series of patients with febrile transfusion reactions than were reported on in our earlier publications [*3,8,12*].

The results of the present survey for antibodies in the serums of 221 patients who suffered febrile transfusion reactions emphasize the marked frequency with which leukoagglutinins are found in such patients. The current finding of 67 per cent of persons with leukoagglutinins in 221 patients with febrile transfusion reactions is in good agreement with both our own previous report of 65 per cent of forty-nine patients [*3*]

and with van Loghem and colleagues who reported 63 per cent of thirty-eight patients [7]. The incidence of leukoagglutinins (67 per cent) was much higher than that of red cell agglutinins (18 per cent). The significance of the presence of these leukoagglutinins is their capacity to induce febrile transfusion reactions. This was indirectly shown by the successful prevention of reactions with repeated administrations of leukocyte-poor blood to forty patients with leukoagglutinins. The direct evidence derived from inducing reaction with buffy coat was limited to three patients since similar experiences were obtained in other laboratories [2,6]; it seemed superfluous to subject additional patients to this procedure. The 67 per cent incidence of leukoagglutinins in febrile transfusion reactions should be considered a conservative one since the criteria for acceptance of a serum for investigation were not strict. On the other hand, a review of the histories of the patients after the laboratory tests had been completed, showed that the symptoms in many did not fulfill the requisites for a febrile transfusion reaction; in some cases the chills and fever of the patients had preceded the transfusion reflecting the underlying disease rather than the effect of transfusion. While it was not feasible to evaluate all the febrile reactions, if a number of doubtful reactions were excluded from this series, an increase in the incidence of those that could be ascribed to leukoagglutinins resulted. Since the panel of leukocyte types used to screen serums for leukoagglutinins was later shown to be incomplete, this would provide still another reason to anticipate a greater incidence of leukoagglutinin reactions. This was substantiated by the study of a serum from a parous woman with repeated febrile transfusion reactions. Her serum failed to agglutinate any of the test panel but did agglutinate the leukocytes of her husband. Thus the over-all experience in our laboratory would suggest that in future work the proportion of reactions attributable to leukoagglutinins will probably be larger than 67 per cent.

The foregoing comments do not imply that in the absence of red cell antibodies all other febrile transfusion reactions are due to leukoagglutinins but rather that leukoagglutinins are responsible for a large proportion of such reactions. Other agents, plasma constituents and platelets, require more thorough study. Harrington et al. [17] have pointed out that "in recipients with auto- or isoantibodies for platelets, transfusions are occasionally followed by low grade febrile reactions and rarely by shaking chills and high fever." Conley [17] has not seen reactions in thrombopenic patients transfused with platelets [17]. The question of "plasma" transfusion reactions seems to be unresolved. Four of the eleven patients reported on by Dameshek and Neber [18] to have suffered "plasma" transfusion reactions had histories of transfusion compatible with the leukoagglutinin type of reaction. If obstetrical histories for two other patients had been provided these might have suggested that stimulation by fetal leukocytes had been operative. These workers attributed the efficacy of washed cells in treatment to the removal of plasma. The washing process in our experience tends to decrease the number of leukocytes. Repeated washing may have reduced the level of leukocytes to a point which prevented overt reaction. In our opinion, plasma type reactions require reinvestigation to rule out those in which leukocyte antibodies may have been involved.

The current findings that women, in a significantly greater proportion than men, had leukoagglutinin transfusion reactions should not be surprising if the experience with red and white cell antibody formation during pregnancy is recalled. While there may be sex differences other than pregnancy that could contribute to the greater proportion of women, the family studies presented herein on leukocyte antigens very strongly support the concept that these reactions are the consequence of antibody production in women from stimulation by fetal leukocytes. Although it is theoretically possible that other means for sensitization of women may exist, such a process has not yet been identified. In interpreting the statistical significance of eight of nine maternal serums possessing the capacity to agglutinate the leukocytes of family members, it must be kept in mind that 15 per cent of a series of 300 parous women tested in this laboratory possessed leukoagglutinins apparently resulting from fetal stimulation. The probability of obtaining by chance alone eight of nine such cases if the true proportion in all parous women is 0.15 is infinitesimal. Therefore, it could be concluded that the women who reacted to the first transfusion stimulus were previously stimulated by fetal leukocytes. In further support of this hypothesis it was observed that children with febrile transfusion reactions, irrespective of sex, did not exhibit

reactions and leukoagglutinins until they had received numbers of transfusions equivalent to those producing reactions in adult men. The concurrence of an absence of pregnancies and leukoagglutinins in a third of the women with reaction to one or two stimulations by transfusion also supports this concept.

If it is accepted that the women who reacted to their first transfusion stimulus had been sensitized during pregnancy, the question may then be asked, could the women who reacted to their second stimulation by transfusion also have been immunized by their fetal leukocytes? This would seem to be the case. All but one of nineteen women for whom data are available had had one or more pregnancies. (Table IV.) Since none of the men were found to react to their second transfusion stimulus, it would seem unlikely that transfusion alone was responsible for the production of antibodies in these women. In one family of this group it was also shown that the patient's serum agglutinated her husband's leukocytes. Therefore, it would seem that fetal leukocytes could have provided the initial stimulus. If this is assumed to be correct, then two possibilities exist whereby the reaction on the second rather than the first stimulation by transfusion may be explained. One is that antibody was present but not in sufficient quantity to induce reaction. The role of the first transfusion may have been to act as a "booster," in other words to induce an anamnestic response. Similar transfusion reactions in women with Rh sensitization from the fetus after the second transfusion were described by Levine in 1944 [*19*]. Until more is known about leukocyte types it cannot be ascertained whether or not the transfused blood and the husband's blood had a common leukocyte antigen. The circumstances of transfusion and pregnancy for four patients (No. 24, 33, 42 and 43) would fit this supposition of booster effect. (Table IV.) Each showed a long sequence of time between the last pregnancy and the first transfusion stimulus, followed by an appropriately brief period between the first and second transfusion stimuli.

The alternative explanation for a reaction on the second transfusion stimulus is that the first unit or series of units may merely have contained leukocyte types compatible with the recipient and incapable of inducing reaction, whereas the second series of units included the incompatible leukocyte antigen which induced reaction. Two-thirds of the women who reacted to their second transfusion stimulus received a total of more than two units of blood, thus increasing the chance for contacts with an incompatible leukocyte type.

The period of time between pregnancy and reaction for the women who reacted to their very first transfusion or series deserves comment. Five of the women were pregnant at the time of study; there was an interval of from one through five years for four women. (Table IV.) Most striking was the observation that a third of the women had not been gravid for more than ten years. There was a period of thirty-nine years between pregnancy and leukoagglutinin transfusion reaction in one woman whose son was demonstrated to possess an incompatible leukocyte type. These long periods between fetal stimulation and detection of leukoagglutinin after a transfusion reaction are analogous to those for Rh antibodies [*19*]. It would appear that there is a group of parous women who become sensitized during pregnancy and then many years later a leukoagglutinin transfusion reaction develops. The forty-four women reacting to few transfusions were found over a period of two and a half years of investigation. This experience cannot be translated into an estimate of incidence because this type of reaction frequently is not reported. Only when physicians are thoroughly familiar with the leukoagglutinin reaction will there be available information on the frequency after few transfusions. Studies are now in process to acertain how many women may be expected to react early in transfusion therapy by determining what proportion of parous women beyond the child-bearing years still possess demonstrable leukoagglutinins.

From the foregoing data it has become possible to predict with a fair degree of accuracy which new patients with febrile transfusion reactions are likely to have leukoagglutinins before they have been tested. A parous woman reacting to either her first or second series of blood transfusions has almost invariably been found to have a leukoagglutinin if her serum is tested with the cells of her husband. Aside from the latter group of parous women, our original observation that between ten and twenty transfusions were usually required for the development of a leukoagglutinin transfusion reaction [*3*] held true for sixteen of the patients. With the new data it became clear that there was a group of approximately equal numbers of men and women who reacted to fewer than ten transfusions, i.e.,

thirty-nine patients reacted after three to nine transfusions. (Table III.) These comprised 27 per cent of the total number with leukoagglutinins. Our data on the number of transfusions necessary for the development of a leukoagglutinin transfusion reaction are in agreement with the work of Marchal et al. [*20*] who contributed to our understanding of the number of stimulations necessary for leukoagglutinin production in human subjects by using a single leukocyte donor as the stimulus. These workers gave intravenous injections of 75 ml. of citrated blood weekly to six recipients for from twelve to nineteen weeks. Each recipient received blood from only one donor. In four of the six recipients leukoagglutinins first developed for the donor's white blood cells after the seventh transfusion; in the other two leukoagglutinins did not develop at all. While the capacity to agglutinate the leukocytes of a given donor developed after the seventh transfusion, the capacity to agglutinate the maximum number of members of a panel of seventeen leukocyte donors occurred after the ninth to eighteenth transfusion. In estimating the probability of a reaction being due to leukoagglutinins, enumeration of the total number of units of blood administered would be incorrect and misleading. Rather it is essential to count the potential stimulations by blood on separate occasions. For example, if a patient received five units on one day and another five units a week later, this should not be considered as ten stimulations but rather as two separate stimulations, recognizing that the chance of a patient receiving an incompatible leukocyte type would be greater than if the patient received a single unit on two occasions. It is our practice to count the units administered over a five-day period as a single stimulation since the intervening time would have been insufficient for demonstrable production of antibodies. The serums from patients with massive transfusions on a single occasion did not contain leukoagglutinins. A group of fifteen persons who received ten or more units on a single occasion during cardiac surgery were found not to have leukoagglutinins in their serums ten days to three weeks postoperatively. Similar data were obtained from patients with peptic ulcer who had received massive transfusions. This guide in assessing clinically the cause of reaction must in no way be interpreted as a substitute for laboratory confirmation. It would be extremely unwise to assume a leukoagglutinin to be present and neglect to search for the potentially more dangerous red cell antibody. These hints on when to expect leukoagglutinins are useful only when red cell antibodies have been excluded as the cause of reaction. In inexperienced hands the prediction without laboratory confirmation of leukoagglutinins may place an undue burden upon the blood bank in requests for leukocyte-poor blood. The policy of a blood bank should be to screen requests and to insist on laboratory demonstration of leukoagglutinins before undertaking preparation of leukocyte-poor blood.

Since patients with a leukoagglutinin transfusion reaction occasionally exhibited urticaria, allergic transfusion reactions were also studied. The allergic reactions considered here included urticaria, edema or bronchial spasm. Their etiology was presumed to be the presence in transfused plasma of a reagin or atopen, for which a complement existed in the recipient's plasma [*21*]. By this definition, the finding of leukoagglutinins in twelve of fifty-seven, or 21 per cent, of the patients with allergic reactions requires explanation. The leukoagglutinins in all the men, the child, and three of the women may be accounted for in terms of their multiple transfusions. (Tables VII and VIII.) Since the remaining three persons were parous women who had had either one or two transfusions, the source of stimulation would appear to be the fetal leukocytes. The urticarial symptoms in the patients with leukoagglutinins could represent an independent reaction rather than being a part of the leukoagglutinin transfusion reaction. In this context it might be noted that twenty of the patients with allergic reactions but no leukoagglutinins had only one or two transfusions. (Table VII.)

The most encouraging aspect of the study of leukoagglutinin transfusion reactions has been the development of practical means for their prevention. Several simple methods are available and can easily be put into practice in the average blood bank. It would seem to the authors, as it has to other investigators [*1,5,13*], that elimination of the cause of the reaction is to be preferred to suppression of the symptoms by various drugs. It is well known that when suppression technics were utilized, febrile transfusion reactions increased in severity with prolonged and continuous transfusion therapy. The repeated use of leukocyte-depleted blood over long periods for four patients reported on herein did not lead to new reaction problems.

SUMMARY

1. Leukoagglutinins were found in the serums of 147 (67 per cent) of 221 patients with febrile transfusion reactions and 12 (21 per cent) of fifty-seven patients with allergic transfusion reactions. In both types of transfusion reaction the presence of leukoagglutinins could be attributed either to prior transfusions or to pregnancies.

2. The proportion of women (72 per cent) with leukoagglutinin transfusion reactions was significantly larger than the proportion of men (57 per cent).

3. In many women leukoagglutinin transfusion reactions developed after significantly fewer transfusions than men. There were forty-four of ninety women, but none of forty-seven men, with leukoagglutinin transfusion reactions after either their first or second transfusion stimulus.

4. In eight of nine family studies of women in whom leukoagglutinin transfusion reactions developed after the first transfusion stimulus it was shown that the maternal serum agglutinated the leukocytes of the husband and/or the children, thus suggesting that the leukoagglutinin probably developed from stimulation by fetal leukocytes.

5. Leukoagglutinin transfusion reactions were consistently prevented in forty patients by the administration of blood from which the majority of leukocytes had been removed.

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Pituitary-Adrenal Function Following Long-Term Steroid Therapy*

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The suppression of ACTH and adrenal steroid secretion in man by exogenous steroid therapy is well known [*1,2*], and the disastrous consequences of unrecognized steroid-induced hypofunction of the pituitary-adrenal axis during stressful illnesses and surgery have been recorded [*3–5*]. A rational method of preventing steroid-induced suppression must, however, be based on a better understanding of the physiologic mechanisms involved. Both in animals [*1,6*] and in men [*1*] evidence has been presented to show that exogenous steroid suppresses the circulating blood level of ACTH in adrenal insufficiency and decreases the pituitary content of ACTH, but the precise mechanism involved remains obscure. Suppressed pituitary function obviously would lead to adrenal cortical hypofunction, as in hypopituitarism; whether or not exogenous steroid therapy can directly suppress the adrenal cortex is not known

In the following report both adrenal (17-hydroxycorticoid-secreting) and pituitary (ACTH-secreting) functions were examined in sixteen patients who had received exogenous steroid therapy for prolonged periods, and in whom therapy was then withdrawn for periods of one week to seventeen months prior to study. Evidence is presented to demonstrate decreased responsiveness of the adrenal cortex in a number of these patients who were secreting large quantities of ACTH following appropriate stimulation. These data, then, suggest that following long-term steroid therapy the responsiveness of the adrenal cortex to ACTH stimulation may still be decreased when pituitary function has returned to or near normal.

MATERIAL AND METHODS

Sixteen patients (fourteen with rheumatoid arthritis, one with osteoarthritis, and one with gouty arthritis) who had received variable amounts of exogenous steroid were tested. Six control subjects with rheumatoid arthritis of similar age and sex distribution who had not received steroids were also examined in the same manner.

Daily twenty-four-hour specimens of urine were collected (8:00 A.M. to 8:00 A.M.) throughout the testing period, refrigerated, and analyzed for 17-hydroxycorticosteroids (17-OHCS) by the method of Reddy [*7*], and 17-ketosteroids (17-KS) by the method of Drekter and associates [*8*] with modified colorimetry [*9*]. The completeness of each urine collection was checked by creatinine determinations [*10*]; if collections were incomplete the data were omitted from the tables.

After a two-day control period either a two-day test of adrenal function (intravenous ACTH test) or a two-day test of pituitary function (SU 4885 test)§ was carried out. After a succeeding two-day rest period the other test was performed. Thus each complete period of study lasted a minimum of eight days.

Intravenous ACTH Test [*11*]. In this study 25 units of commercial porcine ACTH‖ was dissolved in 500 ml. of 0.9 per cent sodium chloride and infused intravenously from 8:00 A.M. to 4:00 P.M., on two successive days.

SU 4885 Test. A new compound, 2 methyl-1,2-bis (3 pyridyl)-1-propanone was administered orally in 250 mg. capsules in a dose of 750 mg. every four hours for forty-eight hours. It has been shown in man and in experiments using dogs that this drug produced a fall in the secretion and excretion of cortisol (Kendall's compound F) and a rise in 11-desoxycortisol (Reichstein's compound S), presumably by interfering with

§ Ciba (Lots E5902, E5927, E5974).

‖ Upjohn (Lot KR179FG).

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TABLE I
URINARY STEROID RESPONSES OF HEALTHY MEN AND WOMEN TO THE STANDARD INTRAVENOUS ACTH TEST*
Mean (Range) of Urinary Steroid Excretion (mg./24 hr.)

Administration of ACTH	17-Hydroxycorticosteroids		17-Ketosteroids	
	Men	Women	Men	Women
Control day	6 (2–8)	6 (4–9)	14 (8–21)	8 (5–10)
ACTH day (1)†	20 (14–27)	17 (10–26)	11 (4–19)	9 (7–18)
ACTH day (2)†	29 (21–39)	29 (24–40)	18 (9–29)	15 (9–21)

* See text. Includes ten women (twenty to thirty yr. of age) and ten men (twenty to forty yr. of age).
† Values on ACTH days represent increments over control.

11-beta-hydroxylation in steroid biogenesis [*12,13,14*]. If pituitary function is intact, SU 4885 leads to an increase in the total amount of 17-hydroxycorticosteroid material excreted in the urine, presumably because 11-desoxycortisol is not a potent suppressor of ACTH secretion. The rise in urinary steroids during SU 4885 therapy can be suppressed by the concomitant administration of a potent suppressor of ACTH secretion, such as 9-alpha-fluorocortisol [*13,15*]. Therefore, increased adrenal steroid secretion during the administration of SU 4885 is evidence for functional ACTH-secreting tissue in the pituitary. Orally administered SU 4885 was found not to interfere chemically with the determination of total urinary 17-OHCS and 17-KS [*15*].

Samples of plasma (heparinized, separated and frozen within thirty minutes of withdrawal), 20 to 40 ml., were taken just before the first dose of SU 4885 and two to four hours after the last dose. These samples were assayed for ACTH activity in the hypophysectomized dog according to the method of Nelson and Hume [*16*]. Generally, if the sample taken after SU 4885 therapy (theoretically more likely to contain measurable ACTH levels) did not reveal detectable ACTH activity, the sample before SU 4855 therapy was not assayed. It should be pointed out that this method will not detect ACTH activity in normal subjects with the volumes of plasma used and therefore a negative assay would not rule out a small increase of ACTH activity above normal.

RESULTS

For comparison, the urinary steroid values for 17-OHCS and 17-KS in ten healthy women and ten healthy men before and after ACTH infusion are presented in Table I.

The observations on pituitary and adrenal function in three men and three women "control" patients with rheumatoid arthritis who had not received steroid therapy are presented in Table II. When these values are compared with those of Table I, it is apparent that in the older age group (fifty-eight to sixty-five years of age) with rheumatoid arthritis the mean basal excretions of 17-OHCS and 17-KS are in the low range of "normal." After ACTH stimulation this is again true except for the 17-OHCS excretion response on the second day of ACTH administration which is far below the range for healthy subjects. Since insufficient data on the response of "healthy" subjects to the administration of SU 4885 are as yet available, the responses of the patients in Table II to this substance cannot be quantitatively compared, but they all appear to be adequate except for one patient (A. G.). Plasma ACTH was measurable in patient O. E. following the SU 4885 test, probably due to the subnormal responsivity of the adrenal cortex demonstrated by the response to exogenous ACTH.

The data obtained on the sixteen steroid-treated patients are presented in Table III. In six, plasma ACTH was measurable following SU 4885 therapy. All sixteen patients had basal 17-OHCS excretion within the range of "normal" but only six could be so classified with respect to basal 17-KS excretion. In response to exogenous ACTH, four had 17-OHCS responses within the normal range on the first day, and three (of fourteen) responded normally on the second day. Three patients (F. L., L. D. and H. M.) had 17-OHCS responses equal to or exceeding the mean value for the second day of ACTH stimulation in the six control patients who had not been treated with steroids. In terms of 17-KS excretion following the administration of ACTH, seven had responses within the normal range on the first day, but only four (of fifteen) on the second day.

Of the six control patients given SU 4885, three complained of "heartburn." Of the sixteen steroid-treated patients all but two had the following side effects: "heartburn," eleven; increased joint stiffness and pain, six; pyrexia, five; drowsiness, four; nausea, four; vomiting, four; dizziness, two; anorexia, two; general malaise, two; weakness, one.

COMMENTS

That ACTH was present in measurable amounts in the plasma of six of the steroid-treated subjects following SU 4885 therapy clearly demonstrates the ability of the pituitary gland of these patients to produce ACTH. This is

TABLE II

PITUITARY AND ADRENAL FUNCTION IN PATIENTS WITH RHEUMATOID ARTHRITIS NOT TREATED WITH STEROIDS

Patient, Age and Sex (yr.)	Duration of Illness (yr.)	Urinary Steroids (mg./24 hr.)										ACTH Activity in Plasma (milliunits per 100 ml.)	
		Control Days		Increment on									
				25 Units ACTH				4.5 gm. SU 4885					
				17-Hydroxy-corticosteroids		17-Keto-steroids		17-Hydroxy-corticosteroids		17-Keto-steroids			
		17-Hydroxy-corticosteroids	17-Keto-steroids	Day 1	Day 2	Day 1	Day 2	Day 1	Day 2	Day 1	Day 2	Before SU 4885	After SU 4885
O. P., 58, M	1.5	4.8	11.5	...	7.7	...	11.3	2.0	...	5.0	...	...	0
A. G., 61, F	21	4.2	6.0	6.5	5.9	0	3.2	−0.1	...	−0.5	...	...	0
F. M., 62, F*	14	2.4	3.4	8.5	12.2	2.6	10.4	4.0	15.2	1.1	6.5	...	0
N. M., 62, M*	1.3	6.1	10.4	15.7	16.4	12.3	15.9	2.5	20.5	2.4	26.9	...	0
O. E., 50, M	10	4.4	14.2	7.8	...	6.6	7.4	0.5	10.5	−5.2	10.6	...	6
H. C., 65, F*	10	2.9	4.9	13.2	9.4	5.6	8.4	...	6.9	...	7.6	...	0
Mean	...	4.1	12.0† 4.8‡	10.3	10.3	5.4	9.4	1.8	13.3	0.6	12.9	...	...

* Had SU 4885 test before ACTH test. † Male. ‡ Female.

of added importance since four of the six steroid-treated patients (F. C., E. H., M. T. S. and D. T.) in whom ACTH was demonstrable had urinary steroid responses to exogenous ACTH which were both below the normal range (Table I) and the mean of patients not treated with steroid (Table II). Plasma ACTH was measurable in one subject (O. E.) of the control group but he also had subnormal responsivity to exogenous ACTH.

The significance of these observations lies in the demonstration of adequate pituitary function in patients who have decreased adrenal responsiveness to exogenous ACTH or to the SU 4885 test. If it were not now possible to measure plasma ACTH levels it might have been assumed that adrenal responsiveness was poor because of lack of endogenous ACTH secretion. The determination of urinary corticosteroids, after administration of SU 4885, demonstrates adequate pituitary activity in those patients whose adrenals are responsive to ACTH but is not effective as a test of pituitary function in the non-responsive group unless plasma ACTH also is measured.

The SU 4885 test increases the probability of demonstrating ACTH in the plasma because of the increased adrenal secretion of 11-desoxycortisol and the decreased secretion of cortisol. Lack of cortisol, then, acts as a stimulus to ACTH secretion, as it does in the adrenalectomized subject. Therefore, following exogenous steroid therapy, the pituitary (i.e., ACTH secretion) may be suppressed to a lesser extent or recover more quickly than the adrenal cortex. Previous clinical studies [*13,17*] have reported normal ACTH content in the pituitary glands of patients with adrenal atrophy who had received steroids until the time of death. Recently, it has been reported [*4*] that when cortisone was withdrawn from cortisone-treated rats the pituitary content of ACTH returned to normal levels in ten days, but adrenal atrophy persisted. Other workers, however, [*19,20*] have presented evidence which suggested that the pituitary-hypothalamic system may be severely depressed by exogenous corticosteroids. If, as is demonstrated by these data, adrenal responsivity is still low in many patients previously treated with corticosteroids but with return to normal of pituitary function, additional consideration should be given to the simultaneous administration of ACTH to patients receiving corticosteroids. As is well known, in animals [*4–18*] and man [*3*] treated with corticosteroids concomitant ACTH administration prevents adrenal atrophy

TABLE III

PITUITARY AND ADRENAL FUNCTION IN PATIENTS TREATED WITH STEROIDS

Patient, Age and Sex (yr.)	Major Illnesses	Estimate o. Exogenous Steroid Therapy				Urinary Steroids (mg. per 24 hr.)									ACTH Activity in Plasma (milliunits per 100 ml.)	
						Control Days		Increments on								
								25 Units ACTH				4.5 gm. SU 4885				
								17-Hydroxy-corticosteroids		17-Keto-steroids		17-Hydroxy-corticosteroids		17-Keto-steroids		
		Type	Dose (mg./day)	Months On	Months Off	17-Hydroxy-corticosteroids	17-Keto-steroids	Day 1	Day 2	Day 1	Day 2	Day 1	Day 2	Day 1	Day 2	Before SU 4885	After SU 4885
R. L., 67, F	Rheumatoid arthritis 19 yr., inactive	Various	...	12	15	5.8*	6.5*	3.8	23.8*	−1.5	8.6	1.4	7.5	−1.2	1.1	0	0
F. C., 53, F	Rheumatoid arthritis 11 mo., active	Cortisone	150–200	2.5	18d	3.0	8.4*	5.6	8.9	3.0	1.7	3.6*	...	−1.7	...	0	12
E. H., 67, F	Rheumatoid arthritis 17 yr.; T.B., right knee	Prednisone	7.5-10	36	1	3.0	4.3	6.9	6.3	1.8	1.5	1.4	...	−1.9	...	0	7
M. T. S., 76, F	Rheumatoid arthritis 25 yr., inactive	Prednisone	10–20	24	3	5.1*	4.7	4.6	3.7	−1.7	0.4	1.0	2.6	−1.2	−0.2	0	4
F. L., 46, M	Rheumatoid arthritis 9 mo., active	Various triamcinolone	12–16	6	7d	9.4*	13.7*	13.7*	12.4*	1.1	−2.1	15.0*	14.1*	1.4*	0.1	0	0
D. T., 45, F	Rheumatoid arthritis 17 yr., active	Cortisone, prednisone	200 50	72	17	4.5*	3.6	4.7	9.8	−0.1	2.4	1.9*	1.7	−1.8	1.0	0	5
T. S., 44, M†	Rheumatoid arthritis 8 mo., active	Cortisone, prednisolone	75 12	1 3	28d	5.8*	9.9	12.9*	21.1*	7.3*	16.4*	−0.4	11.2	7.7*	11.4	0	0
A. T , 56, M	Rheumatoid arthritis 10 yr., active	Various prednisone	20	60	3	5.6*	6.7	0.7	3.3	0.9	6.9	−3.6	−2.5	4.4*	3.5	...	0
R. C., 59, F†	Osteoarthritis psoriasis	Prednisone, 6-methyl-prednisolone	15–20 8	4 10	18d	2.8	5.0*	9.3	8.6	14.2*	17.3*	−1.6	11.0	−2.7	18.4*	...	0
F. T., 56, F	Rheumatoid arthritis, active	Cortisone, prednisone, cortisol	50 40	66	18	3.0	2.8	7.0	...	3.3	3.5	2.0*	7.4	1.5*	12.3	...	0
M. S., 46, M	Rheumatoid arthritis 1 yr., active	Prednisone, prednisolone	30 10	8 1	42d	6.1*	6.5	4.3	8.8	4.4	4.3	0.1	5.3	1.9*	0	...	0
E. B., 56, F†	Rheumatoid arthritis 9 yr., inactive	Various, (3 tablets per day)	...	3	7	2.6	2.9	2.4	8.2	−0.4	1.1	0.9	4.2	−0.9	3.3	...	0
L. D., 69, M†	Rheumatoid arthritis 1 yr., active	Prednisolone	25	8	7d	2.6	2.6	9.1	10.3*	6.8*	8.0	2.1*	...	0.5	...	...	0
L. L., 68, F†	Rheumatoid arthritis 3 yr., active	Prednisone, triamcinolone	15 12	34	21d	.8*	4.2	14.7*	...	9.0*	...	0.3	8.2	0.3	4.8	0	9
H. M., 55, F†	Rheumatoid arthritis 3.5 yr., active	Cortisone, prednisone	200 20	42	24d	4.4*	4.4	7.8	14.0*	3.7	7.4	1.8*	7.7	−0.8	3.0	0	8
H. O., 54, M†	Gouty arthritis	Various, (2–8 tablets per day)	...	84	28d	2.1	4.5	17.0*	28.7*	10.0*	13.6*	3.9*	12.0	−0.4	1.9	0	0

NOTE: d indicates day
* Value equal to or exceeds mean of control group (Table II).
† Had SU 4885 test before ACTH test.

or maintains adrenal responsivity to intravenous ACTH.

It is of interest that the non-steroid-treated control group showed "low normal" basal steroid excretion and "subnormal" adrenal responsiveness to ACTH. That this is secondary to the general debilitation of rheumatoid arthritis is suggested by the fact that one patient (N. M.), who had the disease only fifteen months (shortest time for the control group), had the best urinary steroid response to both ACTH and SU 4885 therapy. On the other hand another patient (A. G.), who had the disease for twenty-one years (longest time for the control group), had the poorest response to ACTH. It is apparent that poor ACTH responses in debilitated and elderly patients must be interpreted with caution.

In all of the sixteen steroid-treated patients the basal urinary excretion of 17-OHCS was within the low normal range, but in the majority the responsiveness to ACTH was distinctly subnormal. The degree of impairment in response to ACTH did not seem related to age, sex, duration of steroid therapy or period of steroid withdrawal. However, those who responded poorly had been ill for a longer period of time. Thus chronic illness profoundly influenced adrenal responses, but whether or not this is peculiar to rheumatoid arthritis is not known.

Of interest were the side effects of SU 4885 therapy which appear to fall in the following three categories: (1) Local effects on the gastrointestinal tract. These symptoms could usually be avoided by giving food and antacids concomitantly. (2) Depression of the central nervous system. (3) Exacerbation of active rheumatoid arthritis. In one patient (L. D.), SU 4885 therapy was discontinued after eight doses because of marked pyrexia and increased arthritis. None of the patients with clinically inactive arthritis experienced joint symptoms after the administration of SU 4885.

Since SU 4885 therapy induces a shift in the production of adrenal steroids from cortisol to 11-desoxycortisol, a weak glucocorticoid, it was anticipated that acute adrenocortical insufficiency might have occurred during administration of the compound. We have previously observed shock during an SU 4885 test carried out in a young woman with nephrosis shortly after discontinuance of steroid therapy; she recovered promptly after the intravenous administration of cortisol hemisuccinate. The blood pressure should be checked frequently in such patients receiving SU 4885, and evidence of adrenal insufficiency should be looked for carefully. However, none of the patients of this group receiving SU 4885 had any significant fall in blood pressure.

SUMMARY

Following exogenous steroid therapy, pituitary function (ACTH secretion) may recover more rapidly than adrenocortical function. The failure of many patients so treated to secrete adrenal steroids in adequate amounts, even months after withdrawal of therapy, indicates the need for periodic investigation of adrenal function, and periodic ACTH administration to patients receiving long-term steroid therapy.

Chronic illness, such as rheumatoid arthritis reduces the steroidogenic responsiveness of the adrenal cortex to ACTH.

SU 4885 (2 methyl-1,2-bis (3 pyridyl)-1-propanone) may be used as a means for evaluating pituitary function (ACTH secretion) by measuring urinary corticosteroids in those patients whose adrenals are responsive to exogenous ACTH. If plasma ACTH is determined, SU 4885 therapy may also be a useful tool in estimating the capacity of the pituitary gland to secrete ACTH in patients who produce some corticosteroids but whose adrenals are relatively unresponsive to stimulation by ACTH.

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Recurrent Attacks of Bacterial Meningitis*

A "New" Clinical Problem. Report of Five Cases

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WITH the dramatic lowering of the mortality rate of bacterial meningitis since the introduction of antibacterial agents, multiple attacks of bacterial meningitis no longer are a curiosity. In the majority of these cases there has been a previous injury to the head and as a result of this a cerebrospinal fistula has developed. The danger of infection of the meninges with bacteria from the nose and throat is then obvious. It is less well known that multiple attacks of bacterial meningitis may be the only indication of the existence of an abnormal communication between the nasopharynx and the meningeal space and that such a communication *must* be found, even if it does not give rise to rhinorrhoea or make itself felt in any other way, and even though neither a fracture nor pneumatocele can be demonstrated roentgenologically.

As such a pathological communication between the meninges and the rhinopharynx is nearly always post-traumatic, this problem now has greater clinical and medicolegal interest, in view of the steadily increasing number of traffic accidents and subsequent claims for damages. The medicolegal aspect of this problem may be rather complicated, as there may be a very long lapse between the time of the head injury and the occurrence of the first of the multiple attacks of meningitis.

Even before the advent of antibiotics Bronstein [*1*] described a case of recurrent meningitis. The original attack was associated with a nasal operation. The recurrent attacks took place four and six months later; the final attack occurred after a lapse of seven years. The causative organisms varied, but at no time was the presence of meningococci definitely established. An autopsy was not performed. It should be noted, however, that the second and the third attacks were associated with a nasal discharge. The first of these attacks could very well have been a relapse, while the last, because of the long free interval, may well have been a true new attack.

Craddoch and Browers [*2*] reported on a patient who had suppurative meningitis four times within a year. Two different types of pneumococci were found on the first and third admission, so there must have been at least two separate infections, possibly four; at least three attacks may also have been flare-ups of a dormant focus.

Traut [*3*] described a girl who had her first attack of meningitis when she was seven years old, two and a half years after she had a fracture of the skull. Later, in the course of four years, she had a total of five attacks of meningitis. Three of the attacks could possibly be considered relapses rather than new infections as the same type of pneumococcus (type 21) was recovered each time. However in the fifth attack, a different type, 15, was found. Fox [*4*] reported cases clearly illustrating the distinction between relapsing and recurring meningitis.

At the beginning of the antibiotic era Hoyne and Schultz [*5*] described, as a great rarity, a case in which the patient had meningitis five times in the course of five years. On each occasion a different organism was found in the spinal fluid. When the patient died following his fifth infection the autopsy clearly afforded an explanation for the vulnerability of the meninges: two small perforations were found behind the Crista Galli leading into the ethmoid air cells and so to the nasopharynx. It should be noted that the patient had fallen from a scaffold eleven years before his first admission. X-ray films of the skull at that time did not disclose any fracture; neither did the history give any information as to whether there had been rhinorrhoea. The authors also point out that when establishing a diagnosis of pneumococcal meningitis (non-recurring) they

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had often been impressed by the patient having had a fracture of the skull or an injury to the head long before.

Mollaret [*6*] described recurrent "aseptic" types of meningitis under the name of "méningite endothélioleucocytaire multirécurrente bénigne." The finding of large clear endothelial cells in the spinal fluid is characteristic. The meningitis is, as the name implies, benign, and it does not seem to show any relationship to previous injury to the head or to craniopharyngeal fistula. However, in some cases of this type of meningitis [*7*] the cell count may be so high as to be mistaken for a bacterial meningitis.

In his excellent article on the treatment of rhinorrhoea and otorrhoea Dandy [*8*] pointed out that in recurrent otogenic meningitis also a fracture of the skull is much more often the cause than congenital malformations. Maxwell [*9*] reported two cases of recurrent otogenic meningitis. One in a five year old boy resulted from a transverse fracture through the petrous bone. At operation it was found that the dura was trapped in the fracture line. The first attack of meningitis occurred one year after the fracture. The mechanism for the occurrence of recurrent meningitis under these circumstances probably is similar to that in rhinogenic cases. It has been repeatedly demonstrated that after fracture through the cribriform plate a small sealed-off vascular cuff of meninges, with or without brain tissue, may be trapped in the old fracture line and, by its vascular connections, provide the avenue of entrance for infection from the nose to the meninges. It would therefore seem quite possible for meningitis to develop late, or to recur, in an analogous situation in the petrous bone.

Prěcechtěl [*10*] states that recurrent meningitis in otorhinolaryngology, after the introduction of modern chemotherapy, "is a new pathologic anatomical problem" and he postulates that in the future we shall see a predisposition to recurrent meningitis mostly in patients with fracture of the base of the skull. Prěcechtěl refers to four patients with recurrent otogenic meningitis, two of whom suffered a striking number of relapses. In a discussion following Prěcechtěl's paper Cawthorne mentioned a case, a boy aged nine, who since the age of four had recovered from eighteen attacks of otogenic meningitis. In this instance there was no history of injury to the head and the reason for the meningeal vulnerability was found to be a persistent petrosquamosal suture. Such a possibility must always be considered even though it seems to be rare in relation to recurrent meningitis of traumatic origin.

Harpman's [*11*] case of recurrent meningitis, which was stated to be of non-traumatic etiology, is not so convincing. The first of the attacks was caused by meningococci, the last three by pneumococci. However, between the first and the second attack the patient had undergone a mastoidectomy and some months later it was stated that his nose was "moist."

Galloway and Chambers [*12*] also strongly stress the significance of trauma in pneumococcal meningitis. They describe seven adult patients in whom previous trauma must be considered to be of significance, even if this trauma occurred a long time (as long as twenty years) before. One of their patients had four attacks of meningitis and they stress the point that in every patient with multiple attacks of meningitis the possibility of some defect of the skull should be borne in mind. In Tribiano's [*13*] case also the first attacks followed an injury to the head. This was in an eight year old boy who, in the course of seven years, had four attacks of pneumococcal meningitis. It is worth noting that it was not at first evident that the head injury had resulted in a permanent atrium of infection. The fourth attack occurred despite attempts at immunization with type-specific polysaccharides.

Barsky's [*14*] reports and those of Ocklitz [*15*] state that it is not always possible to find a fracture or a fluid fistula. Ectors [*16*] indicates one of the reasons why the presence of an open fistula is not necessary in such multiple attacks of meningitis. In his two cases post-traumatic fixation of cerebral tissue in the sinus had occurred. He considers this to be as important as a fluid fistula in the pathogenesis of recurrent post-traumatic types of meningitis. Such a fistula, if it does become apparent, can make itself felt for the first time many years after the injury to the head, as in Winberg's [*17*] well documented case.

Stenger's [*18*] report on recurrent pneumococcal meningitis as a result of "Bagatellverletzungen des Fronto-basalschädels" is also very illustrative in this respect. One of his patients had pneumococcal meningitis five times in the course of three years. The first attack came thirty-one years after an injury to the head that resulted in fracture of the nasal bones; in other respects this injury did not seem to have been serious, and had not given rise to a recognizable

fistula or fracture of the skull. Operation, however, showed that the reason for the recurrent meningitis lay in a defect in the posterior wall of the frontal sinus, together with an adjoining fracture line.

It should be mentioned in passing that in other debilitating diseases which bring with them a tendency to recurrent infections the meninges may, of course, be attacked several times in the absence of any local predisposing factor. One may see this, for example, in chronic leukemia, particularly after treatment with radiotherapy [*19*].

A detailed report of five cases illustrative of the points made will now be given.

CASE REPORTS

CASE 1. A. O., male, born 1907. *First attack:* The patient was admitted to the department with meningitis for the first time on September 10, 1940. Three days previously he had been taken ill suddenly with severe headache and fever. The next day he was delirious and had severe vomiting. The significant events in his past history were as follows: In 1929 he received an injury to the head. He contracted syphilis in 1930 and was treated with Salvarsan,® the blood Wassermann reaction becoming negative at the end of treatment. He was in a sanitorium for four months in 1934 with tuberculosis. In 1937 he was hospitalized because of infiltration of the right lung and right-sided pleurisy. Tubercle bacilli were not found. In 1937 he received another injury to the head; however, nothing pathological was discovered at that time.

Physical examination at the 1940 admission revealed a patient who was well oriented, but tired and weak, and who complained of severe headache. The temperature (rectal) was 38.5°C., pulse 60, blood pressure 150/90 mm. Hg. There was marked nuchal rigidity and Kernig's sign was positive. The remainder of the physical examination revealed no abnormalities. Lumbar puncture gave the following results: Cells 1,000 with polymorphonuclears predominating. Culture of the spinal fluid was positive for Hemophilus influenzae. The urine was within normal limits, and the white blood count was 9,200 per cu. mm.

The patient was given sulfapyridine, 0.5 gm. six times a day for twelve days, together with sedatives. His condition improved rapidly in the course of a few days and the remainder of his stay in the hospital was uneventful. He was free of fever after eleven days and went home, asymptomatic, after forty days in the hospital.

Second attack: The patient consulted a doctor in August 1948 while he was travelling abroad as a seaman. It was first thought that he was suffering from "rheumatism" but he then became very ill and was admitted to a hospital in Belgium with meningitis, and treated there for one month. He was sent home unfit for work and was not able to manage a full time job. The etiology of his meningitis on this occasion is unknown.

Third attack: The patient was readmitted to this department on February 2, 1949. On January 31 he had been taken ill suddenly with vomiting; the next day he had a severe headache and the vomiting was worse. Physical examination revealed a pale and ill man. He was alert, but complained of severe headache. His temperature was 37.6°C., pulse 68. The only important physical findings were nuchal rigidity and a positive Kernig's sign. Lumbar puncture revealed a purulent fluid in which polymorphonuclears predominated. Culture of the spinal fluid was positive for Hemophilus influenzae. On admission sulfadiazine and penicillin were given; the next day penicillin therapy was stopped and streptomycin was added. In all the patient received 66 gm. of sulfadiazine and 9.4 gm. of streptomycin. He was discharged asymptomatic on his thirtieth hospital day.

Fourth attack: The patient was admitted again five weeks later on April 10, 1949. In the previous weeks he had made a good recovery and was on the point of going back to work when, on the day of admission, his head suddenly began to ache severely, and later in the day he felt sick and vomited. He had also had rigors in the hours before he was admitted. Physical examination revealed a restless, semicomatose man. The temperature was 39°C., pulse 94, blood pressure 135/95 mm. Hg, respiration 20. There was nuchal rigidity and a positive Kernig's sign. Lumbar puncture revealed a cloudy fluid consisting almost entirely of polymorphonuclear cells, glucose 28 mg. per cent. Culture of the spinal fluid was positive for pneumococci. Administration of streptomycin was started promptly, and from the second day on he was treated with penicillin 30,000 units six times a day and sulfadiazine 6 gm. daily. The patient became afebrile after four days, and the subsequent course of the illness was uneventful. During his stay in the hospital he was found to have a positive blood Wassermann test and he was given an additional course of 5 million units of penicillin. During this admission roentgenological examination also was carried out to see if there was a fracture of the skull, but the results were within normal limits. Otological investigations showed reduced hearing on both sides, most marked on the right. No rhinorrhoea was found, and the history on this point was negative.

Fifth attack: The patient was readmitted on February 14, 1950. He had felt well in the preceding eight months and had worked as an orderly in a mental home. He said that he had had a cold for some time, with a cough and nasal discharge, but that he had continued to work as usual. On February 12 he had attacks of shivering and a severe headache. The next day he vomited, and was admitted once more with the diagnosis of meningitis. Physical examination revealed nuchal rigidity, but Kernig's sign was negative.

Lumbar puncture again yielded a purulent fluid, with 1,400 cells (polymorphonuclears predominating) and glucose of 25 mg. per cent. Culture of the spinal fluid once more was positive for Hemophilus influenzae. The treatment on this occasion was sulfadiazine 6 gm. daily; 45 gm. was given in all. The temperature was normal by the fifth day, and the meningeal signs and symptoms regressed quickly. The subsequent course of his illness was uneventful, and he was discharged on the twenty-fourth hospital day.

Sixth attack: The patient was admitted on April 28, 1950, because of sudden, severe frontal headache, nausea, giddiness, vomiting and rigors. Physical examination revealed a pale but alert and well oriented man who complained of severe headache. The temperature was 37.9°c., pulse 80. Nuchal rigidity was present, Kernig's sign was negative. The spinal fluid was cloudy, containing many cells consisting almost entirely of polymorphonuclears, and culture was positive for Hemophilus influenzae. He was started on sulfadiazine therapy, 6 gm. daily, but with unsatisfactory results; therefore streptomycin was given in addition, intramuscularly and intrathecally. The meningitic signs and symptoms regressed slowly. He was free of fever for the first time on the eighteenth day. Subsequent progress was uneventful. Once again roentgenograms were taken of the skull and sinuses without finding any sign of a fracture. As his Wassermann reaction was still positive he was given a further course of penicillin, 10 million units, before he was discharged.

Seventh attack: During the week preceding admission on June 27, 1950 the patient had had a cold, sore throat and slight cough. On the day of admission a severe headache suddenly developed, he vomited just after this, and had rigors. In addition his neck became stiff. This time also the usual signs of meningitis were found. Lumbar puncture revealed a cloudy fluid, cell count 800 per cu. mm., mostly polymorphonuclears. Culture of the spinal fluid was positive for meningococci this time. Penicillin and sulfadimethine were given intramuscularly, later sulfadiazine was given orally. He was free of fever on the eighth day of illness, and the meningitic phenomena regressed quickly. He was discharged on the forty-second hospital day. Except for the impairment in hearing that has been mentioned before, he was asymptomatic.

Eighth attack: On September 14, 1954, the patient was brought in comatose. Since his previous stay in the hospital he had had many colds, with nasal discharge, but apart from these he had been well in the preceding three years. On the day of admission he had attacks of shivering and felt ill. Later he vomited and was at once admitted to the department for meningitis. Lumbar puncture yielded a very cloudy fluid under greatly increased pressure, polymorphonuclears predominating among the cells. Spinal fluid culture was positive for pneumococci. He was started on a regimen of penicillin (1 million units), sulfadimethine (2 gm. intramuscularly), and streptomycin (0.5 gm.). Later he was given penicillin, 300,000 units eight times a day, streptomycin 0.5 gm. twice a day, and the sulfadimethine was replaced by sulfadiazine 4 gm. daily as soon as he could take oral medication. He was free from fever on the seventh day, and the meningitic signs regressed quickly. Transient manifestations of a lesion in the right cerebral hemisphere were noticed but when he was discharged he was symptom-free, except for his loss of hearing in the right ear. There was a perforation of the right eardrum from an old otitis. Slight rhinitis and deviation of the nasal septum to the left was present. Again x-rays of the skull and sinuses failed to show any sign of a fracture.

Ninth attack: The patient was re-admitted on May 2, 1955. Except for slight colds he had been well. In the weeks preceding admission he had once again had a cold. On the morning of the day of admission he had a headache which increased as the day wore on; it was localized in particular to the back of the head. He had nausea and was at times confused. His relatives, in accordance with previous instructions, brought him directly to the department, and he was admitted at once. He was alert and orientated, and complained of an intense headache. The temperature was 38.1°c., pulse 84, nuchal rigidity was present, Kernig's sign was negative. Lumbar puncture revealed a slightly cloudy fluid, cell count 400 consisting for the most part of polymorphonuclears. Microscopy showed gram-positive diplococci which were thought to be pneumococci. There was no growth from culture of the spinal fluid. (Antibiotics had been administered before the culture was taken.) He was given 1 million units of penicillin, 0.5 gm. sulfadimethine intravenously and 1 gm. streptomycin; later penicillin (4 million units daily), sulfadiazine (6 gm.) and streptomycin (1 gm.). The meningitic phenomena disappeared quickly. His temperature was normal by the fifth day. He was discharged symptom-free. He was advised to have neurosurgical treatment for the cerebrospinal fistula that he was thought to have, but he refused.

Tenth attack: The patient was admitted on November 7, 1957. Since his preceding admission he had been troubled by dizziness. Three weeks before admission he had been ill with a fever and cough; during the last week he had had some nasal catarrh. On the day of admission he had severe frontal headache and fever. On examination he was alert, well oriented and well nourished. The temperature was 39°c., pulse 76, blood pressure 140/90 mm. Hg. There was slight nuchal rigidity, Kernig's sign was negative. Lumbar puncture revealed a cloudy fluid with a cell count of 2,100 cells per cu. mm., polymorphonuclears predominating. Culture of the spinal fluid was positive for pneumococci. He was treated with penicillin, 1 million units eight times and sulfadiazine, 1 gm. six times. The meningitic phenomena regressed rapidly, and he was afebrile by the fifth day in the hospital.

His further progress was uncomplicated. His electroencephalogram was normal on discharge. When he was discharged prophylactic treatment with phenoxymethylpenicillin was initiated.

Eleventh attack: The patient was re-admitted on November 13, 1958. He had continued his prophylactic treatment with penicillin until September 22, 1958. For the two weeks preceding admission he had had a cold slightly productive of sputum and a serous nasal discharge, the same amount from each nostril. In the twenty-four hours before admission he had had headache, increasing vomiting and fever. He looked ill, complained loudly of severe pain in the head, but was alert and well oriented. The temperature was 38.5°c., pulse 80, blood pressure 160/90 mm. Hg. There was slight nuchal rigidity, Kernig's sign was negative. Lumbar puncture revealed a cloudy fluid with a cell count of 3,000 per cu. mm. Culture of the spinal fluid was positive for pneumococci. Again the patient was treated with penicillin together with sulfadimethine intramuscularly. As soon as oral medication became possible he was given sulfadiazine. His condition improved in the course of a few days. He was afebrile after six days in the hospital and the spinal fluid was normal by the fourteenth day. On this occasion also he was advised to undergo neurosurgical treatment but refused.

Twelfth attack: The patient was admitted on April 9, 1959. For the week preceding admission he had had a slight cold. On the day of admission he suddenly had the beginnings of a headache, nausea and vomiting. The temperature was 38.9°c., pulse 76, blood pressure 160/90 mm. Hg. There was nuchal rigidity and a positive Kernig's sign. Lumbar puncture yielded a slightly cloudy fluid, with 600 cells per cu. mm., polymorphonuclears predominating. Gram stain did not reveal any bacteria but culture of the spinal fluid was positive for pneumococci. He was treated with penicillin, and, to begin with, sulfadimethine intramuscularly. Later, when oral medication became possible, he was given sulfadiazine. The meningitic signs and symptoms regressed gradually. He was afebrile by the seventh day in the hospital. This time again he was investigated roentgenologically with regard to a skull fracture, but nothing was to be found. There was bilateral nerve deafness which was almost complete on the right side. There were no other abnormal findings, in particular no rhinorrhoea. His electroencephalogram was normal when he was discharged, on the thirty-third hospital day.

It should be noted that his serum proteins were investigated on many occasions with regard to the possibility of agammaglobulinaemia. The electrophoretic findings were normal. There have not been clinical signs of reduced resistance to infections other than meningitis.

Summary: A fifty-two year old man received an injury to the head when he was twenty-two years old and again when he was thirty, without any evidence of skull fracture. In the course of the last nineteen years he has survived a total of twelve attacks of bacterial meningitis. Five of the attacks were caused by Haemophilus influenzae, one by meningococci, once no causative organisms were found, and the rest of the attacks were caused by pneumococci. The majority of his attacks of meningitis have followed a period of infection of the upper respiratory tract. On no occasion has it been possible to demonstrate a fracture of the skull roentgenologically, neither has a craniopharyngeal fistula been found. The patient has refused neurosurgical exploration and treatment for the fistula that is surely present. He considers himself to be a celebrated personage and introduces himself to the new interns, not without pride, as "meningitis Olsen!"

Case II. H. E., male, born 1939. *First attack:* The patient was admitted to the department for the first time on October 8, 1947. It appeared from the history that he had been completely well until September 20, 1947, when he was run over by a car. He was unconscious and was admitted to the surgical department. There he was found to have a hematoma around the right eye and bruises on the right side of the head and over the right side of the forehead. No fracture of the skull was found roentgenologically. After nine days he was discharged, well, to his home. The diagnosis was concussion and contusions.

On October 10 he suddenly became ill with a headache and vomiting. He was at once admitted, and was found to have a moderately severe meningococcal meningitis which was treated with penicillin and sulfadiazine. The patient improved quickly, but it was noticed that he was rather hard of hearing. On this occasion his loss of hearing was not further investigated.

A claim for compensation from the insurance company was made on the ground that the meningitis was related to the traffic accident but the claim was turned down on the ground that the boy was completely well after the injury and that no fracture had been found.

Second attack: On November 11, 1952, he was readmitted with a severe meningitis. He was comatose and had convulsions. The meningitis this time was due to pneumococci (not typed). He was again treated with penicillin and sulfadiazine. When he was discharged after six weeks in the hospital he was found to be completely deaf. He had to stop attending the usual school and go to a school for the deaf.

Third attack: The patient was readmitted on June 9, 1954. He had then been ill for four days. On admission he was very ill, in coma with convulsions. The temperature was 40.3°c., pulse 80. Again pneumococci

were the cause of his meningitis (not typed). The treatment was the same as before. He was discharged well on September 17.

The question of compensation in connection with his accident was raised once more. There was disagreement among the experts as to the relationship between his attacks of meningitis, his loss of hearing, and the injury. One of us (H. H.) held that a nasocranial fistula must be present and should be treated surgically. This was done (Professor Herbert Olivecrona, Stockholm), and at the operation on November 30, 1955, it appeared that "the under surface of the right frontal lobe was adherent to the back of the frontal sinus, and possibly to the first of the ethmoidal cells as well. In all probability there was a dural defect here and in addition a break in the bone communicating with the frontal sinus. However, as it was thought best not to damage the adhesions in this position too much, a piece of brain substance was once more put over the supposed dural defect after which the whole of the area concerned was covered with a couple of transplanted pieces of muscle and a piece of fascia lata. There cannot possibly be the slightest doubt as to the traumatic aetiology of the patient's recurrent attacks of meningitis . . ." [*20*].

Summary: An eight year old boy sustained a severe injury to the head in a traffic accident. No fracture was found, neither was a fluid fistula noted. Nineteen days after the accident he suffered his first attack of meningitis, caused by meningococci, and five and again six years later he had repeated attacks of meningitis, caused by pneumococci. A claim for compensation based on the likelihood of a relationship between the injury and his attacks of meningitis was turned down. Neurosurgical intervention proved beyond doubt, however, the traumatic etiology of the recurrent attacks of meningitis.

Case III. B. O., male, born 1938. *First attack:* The patient was first seen in this department on December 14, 1948. Two days before admission he had become ill with fever (temperature 38.9°C.). The doctor suspected pneumonia and the patient was treated with sulfathiazol. The vomiting increased, the temperature rose to 40.7°C., headache appeared.

Significant events in his past history included bronchitis at five years of age. At eight years he had had an injury to the head, the details of which could not be obtained as he had not been admitted to a hospital. At four and seven years he had pneumonia, and three months before admission he broke his arm.

Physical examination showed a well nourished boy ten years of age. He was drowsy, appeared to be very ill, and complained of headache. Herpes labialis was present. There was marked nuchal rigidity and Kernig's sign was positive. The temperature was 38.1°C., pulse 120. Lumbar puncture revealed a cloudy fluid, polymorphonuclears predominating, and gram-positive diplococci. Culture of the spinal fluid was positive for pneumococci (Type VIII). He was treated with sulfadiazine and penicillin. By the seventh day in the hospital he was afebrile, and the meningitic signs regressed quickly; however the headache continued for a longer period. He was discharged symptom-free, forty-eight days after admission.

Second attack: On April 15, 1949, he was readmitted complaining of occasional slight headache since his discharge from hospital. Three weeks before admission he had complained of pain in the right ear; however he had gone to school as usual. On the day of admission, while he was on a trip, he suddenly became ill with headache, vomiting and a rise in temperature to 40°C. He was given penicillin by the doctor who sent him to the hospital. Physical examination revealed a boy who appeared to be drowsy and weak, but well oriented. There was nuchal rigidity, Kernig's sign was positive. The temperature was 39.8°C., pulse 136. He had a crop of herpes lesions on his chin and in the angle of the left side of the mouth. Lumbar puncture yielded a very cloudy fluid, with cells composed almost entirely of polymorphonuclears, but no bacteria could be made out microscopically. Culture of the spinal fluid gave no growth. (Penicillin had been administered before he was admitted.) The patient was treated with penicillin and sulfadiazine. The meningitic signs regressed quickly, and he was afebrile by the eighth day. He was discharged, symptom-free, on the thirty-first hospital day.

Third attack: The patient was readmitted on September 19, 1954. Since his previous admission he had complained of occasional headache. He had had a slight cold for a week, and on the day before admission he complained of headache, began to vomit, and his temperature rose to 39.4°C. Physical examination revealed a well nourished sixteen year old boy who was almost stuporous, with cyanosis of the extremities. There was marked nuchal rigidity and Kernig's sign was positive. The temperature was 39.4°C., pulse 112. Lumbar puncture revealed a cloudy fluid with cells consisting almost exclusively of polymorphonuclears. The spinal fluid contained glucose 7 mg. per cent, chlorides 696 mg. per cent. Culture of the spinal fluid was positive for meningococci. He was started on a regimen of penicillin and streptomycin, later sulfadiazine also. The meningitic signs regressed quickly. He was afebrile from the sixth day in the hospital. This time also he had a severe outbreak of herpes around the mouth, and on the left eyelid. The patient was now able to tell us that for a long time, probably several years, he had noticed that at times a clear fluid came from his right nostril. He had thought it was tears. Before he was discharged he was investigated by an otolaryngologist who found deafness on the left and also rhinitis. Roentgenograms of the skull and sinuses showed no sign of fracture. With the exception

of the deafness in the left ear there were no pathological findings when he was discharged on the twenty-sixth hospital day. It was recommended that he be admitted to a neurosurgical unit to be investigated for the fluid fistula that it was thought certain he had.

Fourth attack: The day before readmission on March 7, 1956, while out skiing, he became ill, with headache, vomiting, shivering and increasing confusion. On admission he was stuporous, with marked nuchal rigidity, positive Kernig's sign, temperature 39.5°c., pulse 110, blood pressure 150/95 mm. Hg. Lumbar puncture yielded a cloudy fluid containing many polymorphonuclear cells, glucose 24 mg. per cent. Culture of the spinal fluid was positive for pneumococci. He was treated with penicillin, sulfadimethine (intramuscularly at first), later when oral medication became possible this was replaced by sulfadiazine. The meningitic signs regressed rapidly, and he was afebrile by the fourth hospital day. Again there was a severe outbreak of herpes. An otolaryngologist found no changes other than those noted on his previous admission. He was discharged on the fourteenth hospital day.

Fifth attack: He remained completely well until two hours before admission on January 3, 1958, when he awoke with a severe headache, nausea and vomiting. His neck and his back were stiff, and he was shivering. He looked ill but was well oriented. There was marked nuchal rigidity. A positive Kernig's sign was present. The temperature was 38.9°c., pulse 120, blood pressure 160/100 mm. Hg. The spinal fluid was slightly cloudy, with a cell count of 350 per cu. mm., mostly polymorphonuclears, glucose 47 mg. per cent, chlorides 696 mg. per cent. Gram-positive diplococci were present in the spinal fluid. Culture of the spinal fluid was positive for pneumococci. He was started on penicillin therapy, 8 megaunits daily, sulfadimethine was also given intramuscularly, 4 gm. daily, and later, when oral medication was possible, 5 gm. of sulfadiazine daily. He was afebrile on the sixth hospital day and the meningeal signs subsided rapidly. This time also there was a severe outbreak of herpes. Examination of the skull and sinuses revealed nothing new. He was advised to transfer to a neurosurgical department for exploratory operation, but declined. He was discharged, completely well, on the twenty-sixth hospital day.

Sixth attack: The patient was admitted again on June 9, 1960. He was extremely ill, suffering from meningitis caused by pneumococci. He was treated with penicillin, sulfadimethine and later sulfadiozine. His recovery was uneventful. A recommendation that he be admitted to a neurosurgical unit was again declined.

Summary: The patient suffered an injury to the head at five years of age. When he was ten he had his first attack of meningitis, caused by pneumococci. At eleven years of age he had a second attack. This time no causative organisms could be found (treated with antibiotics before admission). At his third attack, when he was seventeen years old, meningococci were found. His fourth and fifth attacks, at seventeen and twenty years of age, respectively, were both caused by pneumococci. No skull fracture could be demonstrated at any time. Despite many investigations it has never been possible to find a craniopharyngeal fistula. However, the patient occasionally has had clear secretion from the right nostril. Up to the present he has refused neurosurgical intervention.

Case iv. G. N., male, born 1930. *First attack:* In 1947 the patient lost his right eye in a shooting accident. In 1953 he had an injury to the head with severe concussion. A fracture of the skull was suspected but could not be demonstrated on X-ray examination. Apart from this the past history was non-contributory. He had, now and then, noticed watery secretion from the left side of his nose. He could not state with certainty that he had not had similar secretion from the right side of the nose as well. He had felt entirely well until the day before he was admitted, in particular he had not had a cold. On the morning of the day of admission he awakened with a severe headache. The doctor found signs of meningitis and sent him to the department at once. Physical examination showed a well nourished man. He looked very ill, but was alert, and complained of severe headache. The temperature was 39.1°c., pulse 96, blood pressure 115/60 mm. Hg. There was nuchal rigidity and Kernig's sign was positive. Lumbar puncture yielded a cloudy fluid containing many polymorphonuclears, glucose 55 mg. per cent, chlorides 762 mg. per cent, protein (Heller's test positive 1:70). Culture of the spinal fluid was positive for meningococci.

He was treated with sulfadiazine and penicillin and the meningeal signs subsided quickly. He was afebrile by the sixth hospital day. The subsequent course of the illness was uncomplicated. Roentgenograms of the skull showed no sign of a fracture, and no fluid fistula was found during his stay in the hospital. He was discharged, asymptomatic, on the thirty-second hospital day.

Second attack: The patient was readmitted on November 7, 1957. Since his previous stay in the hospital he had noticed that his nose was occasionally stuffy, mainly on the left side. Otherwise he had been entirely well and in full time employment. On the last two days before admission he had had a slight cold. On the day of admission he had increasingly severe headache, nausea and shivering. Afterwards he became increasingly drowsy and withdrawn. Physical examination showed him to be drowsy, complaining of severe headache. There was marked nuchal

rigidity and a positive Kernig's sign. The temperature was 37.5°C., pulse 112, blood pressure 155/60 mm. Hg. Lumbar puncture revealed a cloudy fluid with a cell count of 800 per cu. mm. The spinal fluid contained glucose 29 mg. per cent, chlorides 698 mg. per cent, protein (Heller's test positive 1:180). Culture of the spinal fluid was positive for meningococci. He was treated with penicillin and sulfadiazine, and the meningitic signs subsided rapidly. He was afebrile by the fifth hospital day. His further progress was uncomplicated, apart from the appearance of a penicillin rash on the ninth hospital day. On this occasion also glucose was found in the secretion from the nose. Repeat x-ray investigations failed to show any sign of a fracture. He was discharged, asymptomatic, on the thirty-fourth hospital day.

Third attack: He was readmitted on September 9, 1958. Since his previous admission he had been almost constantly bothered by slight catarrh, mainly on the left side. Otherwise he had been completely well and in full employment. On the night before he was admitted he woke up with a severe headache, had nausea and severe vomiting. His neck and back became stiff. Physical examination on this occasion showed severe meningeal signs; he was drowsy, and complained of severe headache and low back pain. The temperature was 39.6°C., pulse 92, blood pressure 160/60 mm. Hg. Lumbar puncture revealed a cloudy fluid, with cell count of 1600 per cu. mm., many polymorphonuclears and gram-negative diplococci. Culture of the spinal fluid was positive for meningococci. This time also he was started on sulfadimethine administered intramuscularly and, when oral medication became possible, this was replaced by sulfadiazine. In addition he was treated with tetracycline. The meningitic signs subsided quickly, and he was afebrile by the sixth hospital day. Once again no cerebrospinal fistula could be discovered, but it was now considered very probable that one existed. Neurosurgical intervention has been advised, but the patient would rather wait and see. He was discharged, asymptomatic, on the thirty-first hospital day.

Summary: At seventeen years of age the patient lost his right eye in a shooting accident, and at twenty-three he suffered a further injury to the head. No fracture of the skull was found roentgenologically, but he has at times noticed secretion from the left side of his nose, indicating a fluid fistula. Up to the present he has had three attacks of meningitis, at twenty-four, twenty-six and twenty-seven years of age, respectively, all caused by meningococci. To date he has refused neurosurgical intervention.

CASE V. K. G., male, born 1946. *First attack:* The patient was admitted on January 27, 1952. When he was five years old he was run over by a car. Immediately after the accident he was found to have a fracture of the skull. The fracture line was in the frontal bone to the left of the midline; it went into the frontal sinus and forward to the root of the nasal bone. During his stay in the surgical department the patient was slightly febrile, and was treated with antibiotics. He was discharged, symptom-free, after sixteen days in hospital. Since then he had appeared to be completely well until nine days before admission when he caught cold, with a cough. Two days before admission his mother noticed a swelling over his left eye and at the same time she found that the boy's neck was stiff and that he had a temperature of 39.8°C.

Physical examination showed a boy who appeared to be very ill; he was completely confused, emitting loud cries, and had marked opisthotonus. There was twitching of the left arm and leg. Lumbar puncture yielded a very cloudy fluid, with glucose 3 mg. per cent. Culture of the spinal fluid was positive for pneumococci (not typed). Treatment with penicillin was started and sulfadimethine was given intramuscularly, later, when oral medication became possible, sulfatriad was also given. The patient was free of fever on the eighth day. The meningeal signs gradually subsided. However, when he was discharged there was slight anisokoria, the left pupil being larger than the right, and there was a left-sided facial palsy with deviation of the tongue to the right. Roentgenogram of the skull no longer showed any sign of the earlier fracture.

Second attack: He was readmitted on March 3, 1953. Since his previous admission the boy had, on the whole, been well. One month before admission he had complained of pain in his ear, but investigation by an otologist had not shown anything pathological. During the last weeks he had had a slight cold, with some cough and catarrh. On the day of admission he complained of headache, vomited, was febrile, (temperature 39.6°C.) and his neck appeared to be stiff. He seemed to be drowsy. On physical examination there was severe nuchal rigidity, and Brudzinski's and Kernig's signs were positive. Signs of the earlier neurological lesions were no longer demonstrable. Lumbar puncture revealed a very cloudy fluid containing many cells, mostly polymorphonuclears. Culture of the spinal fluid was positive for pneumococci (Type VIII). The same type of pneumococcus was also found in the patient's nose and throat. He was treated with penicillin, sulfadimethine given intramuscularly and later, when oral medication became possible, the sulfadimethine was replaced by sulfatriad. The meningitic symptoms subsided rather slowly but he was afebrile on the twelfth day. He was discharged, symptom-free, on the thirty-seventh hospital day. Prophylactic sulfadiazine treatment was advised.

Third attack: On October 12, 1953, about six hours before he was readmitted to the hospital, he began to

complain of headache, and just after this he vomited. The vomiting increased, and he was admitted to the department in a stuporous condition. There was considerable nuchal rigidity. The temperature was 38.2°C., pulse 120, blood pressure 145/90 mm. Hg. Lumbar puncture revealed a cloudy fluid, with many polymorphonuclears and gram-positive diplococci. Culture of the spinal fluid was positive for pneumococci (Type VIII). This type of pneumococcus was also found in the nose and throat. He was treated once again with penicillin, and sulfadimethine intramuscularly, which was replaced by sulfatriad when oral medication became possible. He was afebrile in the course of a week, and the meningitic signs subsided rapidly. Roentgenograms of the skull and sinuses showed no sign of fracture. He was discharged, asymptomatic, on the thirty-eighth hospital day.

Fourth attack: One week before his fourth admission on February 17, 1954 he had chicken pox and recovered completely. Then on the day of admission he suddenly became ill with severe vomiting. Nuchal rigidity developed, he rapidly became stuporous and was admitted to the department at once. On admission he appeared to be very ill, stuporous with slight opisthotonus. The temperature was 39.8°C., pulse 100. Lumbar puncture yielded a cloudy fluid, under greatly increased pressure, with numerous polymorphonuclear cells and gram-positive diplococci. Culture of the spinal fluid was positive for pneumococci (not typed). Culture from the nasal cavity was positive for pneumococci (Type VIII). He was treated once more with penicillin and sulfadimethine; in addition he was given streptomycin. He was afebrile on the twelfth day, and the meningitic signs subsided slowly. On March 30, 1954, the frontal sinuses were explored operatively. Pus was found at the bottom of the left frontal sinus, and in the bottom of the sinus was a defect with a fistula through which seeped spinal fluid. It was obvious that neurosurgical intervention was necessary, and the patient was therefore transferred to the care of Professor Hebert Olivecrona, Stockholm, who operated on him on April 2, 1954. A dural defect was found in the posterior wall of the left frontal sinus; the defect was about the size of a hempseed. Many local adhesions were found. The dural defect was covered with a piece of muscle, and his subsequent progress was uneventful. The boy has since been well.

Summary: Eight months after a traffic injury resulting in a roentgenologically demonstrated skull fracture, the patient had his first attack of meningitis. After this no fracture could be demonstrated roentgenologically, and neither then nor later was it possible to demonstrate a fluid fistula. In the course of three years the patient survived a total of five attacks of meningitis, all caused by pneumococci. Finally he underwent laparotomy and a cranionasal fistula was found which had not made its presence known in any way other than through the multiple attacks of meningitis.

COMMENTS

The five cases referred to herein illustrate the clinical manifestations of recurrent meningitis and the problems that may arise in this connection.

If there are roentgenological signs of a skull fracture or, even more important, if there is a clinically demonstrable craniopharyngeal fistula, a relationship between the trauma to the head and the meningitis must be considered extremely likely even if a long time has elapsed since the injury. But the relationship may be difficult to demonstrate, as in our Case v. In Stenger's [*18*] case thirty-one years elapsed between the trauma and the first attack of meningitis, and in our first case either eleven or three years intervened. This difficulty becomes even greater as the head injury may apparently be slight and may have gone almost unnoticed [*18*]. It is also important to be aware that in some cases there may be no other signs or symptoms after the injury than the occurrence of multiple attacks of bacterial meningitis. The abnormal communication with the meningeal space, which is of paramount importance in this problem, is almost without exception of traumatic etiology [*8*]. Occasionally operative procedures can be blamed, less frequently erosion by tumors or infections, and rarely congenital abnormalities.

Post-traumatic fistulas into the frontal or ethmoidal sinuses or through the lamina cribrosa are frequently slow to heal, or they may never heal, or they may close and open again periodically. Plum [*21*] has described a case of eighteen years duration, and Fribourg and his co-workers [*22*] have described another of seventeen years, interrupted by shorter periods when the fistula was closed. The pathogenesis is probably the same when an open fistula is not present, but there is a dural defect covered with granulation tissue, either in the form of a "cuff-link" [*23*] or with the dura trapped in the fracture line [*9*].

The special anatomical conditions in this region may lead to the slow healing of such craniopharyngeal fistulas. The floor of the anterior cranial fossa is almost entirely formed by the frontal bone except in the middle where the cribriform plate of the ethmoid lies over the nasal

cavity. The dura covering the plate and the mucous membrane on the nasal side is firmly attached to the bone, and a fracture nearly always results in tearing of the dura and the mucous membrane thus allowing escape of cerebrospinal fluid into the nasopharynx [*24*].

The most important sign connecting the injury and the meningitis is drainage of cerebrospinal fluid from the nose. This is practically always due to a fistula into the frontal or ethmoidal sinus. But this is not entirely pathognomonic. Drainage may occur through the mastoid bone into the middle ear and the eustachian tube [*8,25,26*]. This, however, is exceptional even though recurrent otogenic meningitis is not a rarity [*8–10*]. While it is obviously of the greatest importance to the surgical treatment to be able to localize the pathological communication with the meningeal space, it is of minor importance in the evaluation of a relationship between the trauma and the meningitis.

It is not clear why some patients should continuously have new attacks of meningitis, as in our first case, while others can go for decades without the meninges being affected [*18,21,22*]. It may be that particular drainage conditions are responsible for the ascending infection. But other factors, unknown, may be of significance. In recurrent virus meningitis [*6*] it does not appear that a dural lesion plays a pathogenic role. What these unknown factors are can only be surmised. None of our patients showed any generalized tendency to other infections, in particular there were no cases of hypogammaglobulinaemia.

Dandy [*8*] pointed out that the course of these types of meningitis in which a fluid fistula is present is relatively benign, and he ascribes this to the free drainage through the fistula in meningitis of this type. This is not, however, a general rule. In our experience we often find that the meningitis runs an unusually stormy course. Our Case III illustrates this very well. It seems to be most reasonable to interpret this as the result of a massive infection from the nasopharynx.

The treatment of the attacks of meningitis in our patients did not differ from the usual treatment of bacterial meningitis. But the treatment of the patient must not be considered to be at an end when the acute infection has been brought under control. The patient can be considered cured only after surgical correction of the dural lesion, which one *knows* must be present even if it is not possible to demonstrate it before operation (as in two of our cases). As to the treatment of the fistula itself, the principles laid down by Dandy [*8*] are generally accepted, with the proviso that the fistula should be closed in all cases.

From the medicolegal point of view, in this age of traffic accidents there is increased interest in patients with multiple attacks of meningitis. If a patient with a previous injury to the head has multiple attacks of meningitis one must reckon that the patient received a lasting injury in the form of a dural lesion, and that there is a definite causal relationship between the trauma and the subsequent attacks of meningitis. This causal relationship must be considered to be definite even if a long time has elapsed between the injury and the first attack of meningitis, and even if there have not been related symptoms of any kind, in particular no skull fracture or fluid fistula. The most important pathogenic factor, a dural lesion, is present all the same, and in these cases the multiple attacks of meningitis are the only sign.

SUMMARY

As the antibacterial treatment of bacterial meningitis becomes more effective, patients with multiple attacks of meningitis are more frequently encountered. In the majority of such cases a lesion of traumatic etiology is present in the dura, with a craniopharyngeal fistula, certainly in these days of frequent injuries to the head resulting from traffic accidents.

Five patients with multiple attacks of meningitis are described. One of the patients has to date, in the course of nineteen years, survived twelve attacks of meningitis caused by Hemophilus influenzae, meningococci and pneumococci.

The only clinically apparent sign of damage after injury to the head may be multiple attacks of meningitis. These may first appear after a long interval of complete freedom from symptoms.

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Familial Myocardial Disease*

A Report of Three Siblings, and a Review of the Literature

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OVER the past ten years there has been a scattering of reports in the European literature about familial myocardiopathy, a degenerative disease of the myocardium which affects members of the same family. It makes its appearance most frequently in young adults, but may begin in childhood or in middle age. The clinical manifestations have been entirely cardiac in nature and not different from those of non-familial, non-coronary myocardiopathic disorders such as the myocarditides, amyloid heart and idiopathic cardiac hypertrophy [*1*].

Failure to find a cause for heart disease in a young patient in whom it develops is always a challenging problem. The differential diagnosis must include a number of cardiopathic disorders, most of which are rare. If idiopathic myocardiopathy appears in more than one member of a family, the examiner may be encountering familial cardiomegaly, a term coined by Evans [*2*].

In all myocardiopathies the diagnosis may remain obscure until autopsy. The pathologist is able to assign a cause to many, but some remain idiopathic. Familial myocardiopathy is idiopathic, and is distinguished only by the familial association. The gross anatomical findings consist of hypertrophy and dilatation of the ventricles. The most frequently reported histologic abnormalities are scattered myocardial fibrosis and hypertrophy of individual muscle fibers. The lack of specific pathologic pattern is the greatest obstacle in establishing familial myocardiopathy as a distinct entity.

The purpose of this paper is to report on three siblings with idiopathic heart disease of striking similarity and to call attention to the reported instances of myocardiopathy occurring with familial aggregation. I know of only one paper [*3*] in the American literature describing this condition. The report of more than forty cases in Europe suggests that the paucity of experience with the condition in this country results from failure to recognize it.

CASE REPORTS

CASE I. D. M., a white boy, five years of age, died in 1928 of an illness of two years' duration. He was the oldest of eleven siblings. The events surrounding his birth and early infancy were non-contributory. At three years of age he had sensations of tiredness in the legs, he showed lack of spontaneous activity, and soon swelling of the legs and abdomen developed. Peritoneal paracentesis was performed approximately twenty times before death. Because of orthopnea he could not lie flat during the last eighteen months of life. The attending physician offered no explanation of the symptoms and signs to the parents. Death occurred from sepsis arising at the site of paracentesis.

CASE II. R. M., a boy, born in 1928, was *in utero* at the time of the death of D. M. (Case I). Ostensibly he was well until the age of five when intermittent abdominal pain and bloating of the face, abdomen and feet developed. He was admitted to University Hospitals on July 5, 1933. He was well developed, well nourished and afebrile. Respirations were 20 per minute. There was no cyanosis, clubbing or distention of the neck veins. The lungs were resonant and no rales were heard. The heart was enlarged to percussion; the cardiac rhythm was regular at a rate of 100 per minute, and a diastolic gallop existed. A low pitched apical systolic murmur was described. There was ascites but no facial, scrotal or pedal edema. The liver extended 3 cm. below the costal margin. It was firm, smooth and non-tender. The spleen was not palpable.

Complete blood count and urinalysis were within normal limits. Results of the serologic test for syphilis and the tuberculin skin test were negative. The serum non-protein nitrogen was 52.1 mg. per 100 ml., total cholesterol 259 mg. per 100 ml., and total protein 6.7 gm. per 100 ml. Roentgenograms of the chest showed a cardiac transverse diameter of 11 cm. compared to 20 cm. diameter for the chest. An upper gastrointestinal x-ray series revealed no abnormalities.

On the ninth hospital day his temperature rose to 101.6°F. and the pulse to 122 per minute. The white

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blood count on the eleventh hospital day was 16,450 per cu. mm. No signs of a specific infection were found and on the twelfth hospital day the temperature returned to normal and remained there. He was discharged on August 4, 1933, with a diagnosis of congenital malformation of the heart, with decompensation.

He was admitted again from May 12 to June 10, 1935. Abdominal paracentesis had been performed seventy-one times after the previous admission, often at four-day intervals with withdrawal of "4 to 8 quarts" of fluid each time.

The blood pressure on this examination was 106/58 mm. Hg, pulse 122 per minute, temperature 98.4°F., and respiration 22 per minute. The lips were slightly cyanotic. Dullness was noted over the left chest below the fourth intercostal space in the midaxillary line. The breath sounds were suppressed in this area but elsewhere were normal. There were no rales. Auscultation revealed a diastolic gallop and accentuation of the pulmonic second sound. The abdomen was tensely distended with fluid. After paracentesis the liver edge could be felt 5 cm. below the right costal margin but the spleen was not palpable.

The results of urinalysis were normal. The hemoglobin was 10.4 gm. per 100 ml., red blood cells 6.59 million per cu. mm., white blood cells 20,700 per cu. mm. with 65 per cent polymorphonuclear neutrophils, 1 per cent eosinophils, 29 per cent lymphocytes and 5 per cent monocytes. Roentgenograms of the chest confirmed the left pleural effusion, which obscured the left heart border. A lateral view showed "the heart to be greatly enlarged in its anteroposterior diameter." Roentgenograms of the abdomen after pneumoperitoneum revealed no enlargement of the liver or spleen. Cardiac fluoroscopy revealed enlargement and rounding of the heart with reduction in the magnitude of its pulsations.

Pericardiocentesis was attempted both anteriorly and posteriorly but no fluid was obtained and the operator recorded that it felt as though the needle passed through thick leathery material.

The ascitic fluid contained 0.55 per cent protein. Its specific gravity was not recorded. Adhesive pericarditis with pericardial effusion and inflow obstruction of the venae cavae was finally proposed and surgical exploration of the pericardium was recommended. Permission for operation was refused and the patient was sent home where he died a short while later. An autopsy was not performed. The parents stated later that the illnesses of these two boys were "identical."

CASE III. C. D., born in 1924, was a sister of the two patients just described. She was admitted to University Hospitals December 16, 1957. She was a thirty-three year old nulliparous housewife with the chief complaints of abdominal swelling for three months and fever for five days. Her general health had been good before the onset of the present illness. About eight years earlier she had had abdominal enlargement and cessation of menses, causing both her and her physician to conclude that she was pregnant. Eight months later it was realized that she had had ascites instead. The swelling gradually subsided and irregular menses reappeared. Her exceptionally stable personality makes the possibility of pseudocyesis seem unlikely. Her menstrual history was normal before this episode but six years before admission menstruation permanently ceased. Two years before admission malaise, anorexia, diarrhea and scleral icterus developed. All symptoms disappeared after a few weeks of reduced physical activity.

She felt well until the summer of 1957 when she noted epigastric pain and vomiting seemingly induced by exertion. This occurred repeatedly. Ankle edema appeared in September 1957 followed shortly by abdominal enlargement. She was hospitalized elsewhere and reported to have a gallop rhythm, "acute carditis" and enlargement of the liver. The electrocardiograms were "abnormal."

Five days before admission her temperature rose to 103°F. and she had mild diarrhea and vomited. On admission to University Hospitals her blood pressure was 140/85 mm. Hg, temperature 102°F., pulse 116 per minute and respiration 20 per minute. She was well developed and well nourished. The scleras were clear. There was distention of the neck veins in the upright position. There was a systolic precordial heave which was visibly transmitted to the entire body. The left border of cardiac dullness was midway between the mid-clavicular and the anterior axillary lines. There was a sinus rhythm with a protodiastolic gallop. The pulmonic second sound was louder than the aortic and a grade 2 systolic murmur was heard at the left sternal border. No other murmurs were audible. A paradoxical pulse was not demonstrable. The liver edge descended 4 to 5 fingerbreadths below the right costal margin and was firm, smooth, and non-tender. The abdomen was distended and shifting dullness was demonstrable. There was edema over the sacrum but no edema of the extremities.

Results of urinalysis were negative. The hemoglobin was 9.3 gm. per 100 ml., and white blood cells 7,050 per cu. mm. with 72 per cent polymorphonuclear neutrophils, 2 per cent basophils, 18 per cent lymphocytes and 8 per cent monocytes. The erythrocyte sedimentation rate was 35 mm. per hour (Westergren). The platelet count was 172,000 per cu. mm. The serum total protein was 6.3 gm. per 100 ml., with albumin 4.1 gm. and globulin 2.2 gm. per 100 ml. The cephalin flocculation was zero at forty-eight hours, the thymol turbidity 1.6 units, alkaline phosphatase 1.9 Bodansky units, total bilirubin 2.9 mg. per 100 ml., blood urea nitrogen 18 mg. per 100 ml., creatinine 1.5 mg. per 100 ml., protein-bound iodine 7.8 μg. per 100 ml., serum sodium 136 mEq. per L., potassium 4.6 mEq. per L., chloride 108 mEq. per L., CO_2 con-

tent 25 mEq. per L., C-reactive protein 4 plus, antistreptolysin "O" titer 2,560 units, and results of a lupus erythematosus cell test were negative. Throat culture yielded a moderate growth of beta hemolytic streptococci. First and second strengths of purified protein derivative (0.0002 mg. and 0.005 mg.) provoked no skin reactions. Cardiac fluoroscopy revealed generalized cardiomegaly. An upper gastrointestinal roentgenographic study showed no esophageal varices or other lesions. Three electrocardiograms were taken during this hospital stay, the first showed a wandering pacemaker, intermittent first degree A-V block and digitalis effect; the others showed atrial fibrillation, complete right bundle branch block and digitalis effect.

The temperature returned promptly to normal with the administration of 2.4 gm. of acetylsalicylic acid per day, but symptoms of salicylism appeared and the drug was discontinued without recurrence of fever. Abdominal paracentesis yielded 4,000 cc. of yellow fluid with a specific gravity of 1.016. The spleen was palpable three fingerbreadths below the left costal margin after the paracentesis. The culture of ascitic fluid was negative as was the result of cytologic examinations. Four blood cultures were taken on admission, and administration of penicillin and chloromycetin® was begun because of a strong suspicion of subacute bacterial endocarditis. The cultures remained sterile and the antibiotics were discontinued on the twelfth hospital day.

She did not improve after full digitalization, and the administration of mercurial diuretics and ammonium chloride were ineffective. Venous pressures of 24.5 and 40 cm. of water, arm-to-tongue circulation times of twenty-five and twenty-four seconds and arm-to-lung circulation times of twenty-three and twenty-eight seconds were obtained on two occasions. She had an acute hemolytic episode early in the hospital course, characterized by scleral icterus, acholuria, fall in hematocrit to 24 per cent, reticulocytosis of 12.8 per cent, and marked erythroid hyperplasia of the bone marrow. The stools contained no occult blood.

Cardiac catheterization on January 21, 1958, revealed the following: a mean right atrial pressure of 17 mm. Hg, right ventricular pressure of 35/12 mm. Hg, pulmonary artery pressure of 35/15 mm. Hg, and a mean pulmonary artery wedge pressure of 15 mm. Hg. The hemoglobin oxygen saturation of the right cardiac chambers and of a systemic artery were normal. An analysis of the pressure pulses did not show the early diastolic dip and rapid rise to a diastolic plateau which is frequently seen in constrictive pericarditis. These findings were interpreted as compatible with right ventricular failure of unknown cause.

She was discharged without a definite diagnosis and shortly thereafter went to the Mayo Clinic. The examiners there agreed that a diffuse myocardial disease was most likely, but they were of the opinion that a constricting pericardium had not been definitely excluded. Consequently, exploration of the pericardium was carried out through a small incision which preserved the integrity of the left pleural cavity. The pericardium was normal and the pericardial space was found to be entirely free of adhesions.

Her second admission to University Hospitals was from May 16 to June 19, 1958. There were no significant changes in the physical findings or routine laboratory examinations except for thrombophlebitis of the lower extremities, for which she was treated conservatively for four weeks. Results of the serum proteins, zinc turbidity and thymol turbidity tests remained normal. On June 13 abdominal exploration was performed. Approximately 6,000 ml. of straw-colored ascitic fluid was encountered. A finely nodular liver was biopsied. The portal vein pressure was 300 mg. of saline solution, the same as the systemic venous pressure, and therefore not indicative of portal hypertension. An attempted splenoportogram was unsuccessful because of rapid disappearance of dye from the portal system. Exploration of the entire abdomen and a biopsy specimen of the retroperitoneal tissues revealed no other abnormalities. The biopsy specimen of the liver revealed good preservation of the general architecture, a definite increase in the amount of intralobular connective tissue, and several nodules of regenerating liver cells. Minimal proliferation of bile ducts and scattered collections of chronic inflammatory cells were noted. No evidence of specific infection or neoplasm was seen.

She was admitted a third time from July 17 to July 23, 1958. She had grown weaker and fatigued more easily. Ascites had developed faster than before laparotomy, requiring several paracenteses. The legs had been swollen constantly. The only new finding was anasarca below the thorax.

The fourth and final admission was from September 9 to October 28, 1958. She had had orthopnea for the first time two weeks earlier. The administration of chlorothiazide and mercurial diuretics had been ineffective. She was emaciated and edema reached to the axillas. Distention of the neck veins in the upright position persisted. There was dullness to percussion and absence of breath sounds at both lung bases. A protodiastolic gallop was heard. The abdomen was tense with ascites. Results of urinalysis were negative. The hemoglobin was 11.2 gm. per 100 ml. and the white blood cell count was 7,850 per cu. mm. Roentgenogram of the chest revealed bilateral pleural effusion. The electrocardiogram was unchanged except for the appearance of an intermittent nodal rhythm. The serum sodium ranged from 116 to 132 mEq. per L. and the serum chloride from 87 to 109 mEq. per L. during the final month of her life. The serum total protein was 5 gm. per 100 ml. with an albumin of 2.1 gm. and a globulin of 2.1 gm. per 100 ml. The cephalin flocculation test was 3 plus at forty-eight hours. Results of another lupus erythem-



FIG. 1. Case 1. Dense scar in the myocardium.

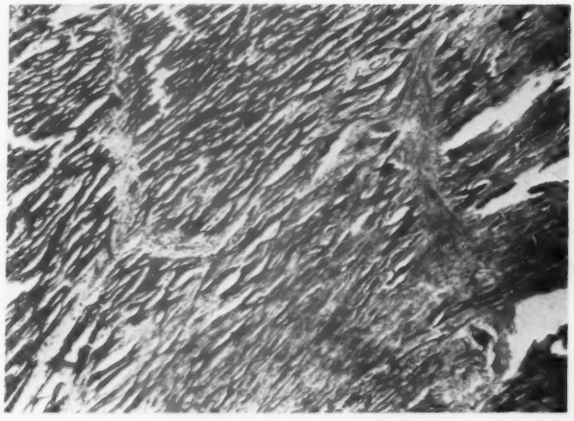


FIG. 2. Case 1. Microscopic view of the myocardium showing patchy fibrosis, some swollen and pale muscle fibers with reduced numbers of cross striations, and other markedly hypertrophied muscle fibers.

atosus cell preparation were negative. Serum electrophoresis on September 12 revealed albumin 57.1 per cent, alpha-1 globulin 6 per cent, alpha-2 14.2 per cent, beta 12.5 per cent, and gamma 10.2 per cent.

She became increasingly dyspneic and cyanosis appeared. Withdrawal of fluid from the chest and from the abdomen was followed by much relief. Cultures of pleural and ascitic fluids gave negative findings. Several diuretic agents were tried, alone and in combination, and efforts were made to correct the hyponatremia. These measures were generally ineffective. She remained afebrile, but complained constantly of weakness and pain in the upper part of her abdomen. She died suddenly on the fiftieth hospital day.

An autopsy revealed that the external contour of the heart was not unusual. The weight of the heart was 270 gm. The right atrial wall was approximately twice the normal thickness. The endocardium was smooth and shiny; the valves were normal. There were no mural thrombi. The coronary arteries were not narrowed. A cut section of the myocardium revealed numerous areas of dense white fibrous tissue. A sheet of fibrous tissue approximately 1.5 mm. thick spread around the left ventricular wall a short distance from the endocardium. (Fig. 1.) Microscopically, there was patchy fibrosis scattered throughout the myocardium. (Fig. 2.) Variable numbers of intact muscle fibers were present in the scarred areas. Some muscle fibers appeared swollen and pale with reduced numbers of cross striations; many muscle fibers were markedly hypertrophied. Vacuolization of the hypertrophied muscle fibers was noted. Special stains showed no excess glycogen. No appreciable inflammatory response was seen in any area.

The liver weighed 1,860 gm. Its surface was finely pebbled and gray in color. Microscopically there was an increase in the perilobular tissue and occasional slight bile duct proliferation. (Fig. 3.) The central parenchymal cells showed some atrophy and the sinusoids were engorged with red blood cells. These findings were interpreted as being consistent with mild portal cirrhosis and chronic passive congestion.

The ovaries and endometrium were atrophied. No corpora albicantia or primordial follicles were seen on microscopic section. The pituitary gland was normal.

The left lung was the site of an extensive necrotizing pneumonitis. Microsections revealed innumerable acid-fast rods and Langhans giant cells. Guinea pig inoculation confirmed the presence of Mycobacterium tuberculosis. Acid-fast stains of the myocardium revealed no tuberculous lesions.

The peritoneal cavity contained 4,700 cc. of cloudy yellowish fluid from which hemolytic Staphylococcus aureus was cultured. The peritoneal surfaces were coated with a shaggy, fibrinous exudate. Sections of the abdominal viscera revealed no granulomatous changes at the peritoneal surfaces.

Summary of Case Histories. Two brothers and a sister, born in 1923, 1924 and 1928, died of

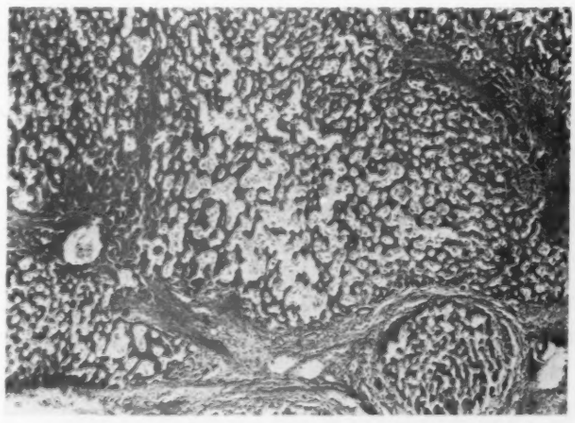


FIG. 3. Case 1. Microscopic view of a section of the liver showing an increase in the perlobular tissue, central atrophy and engorgement of the sinusoids with blood.

strikingly similar conditions. Details of the first patient's illness are not known. The second was studied carefully by the technics available twenty-five years ago, however, he was not explored surgically nor was an autopsy performed. The last sibling to die (Case III) was studied extensively before death and also at autopsy. All patients had slowly progressive ascites requiring frequent abdominal paracentesis. It has been established that all three had good diets during childhood. No evidence of exposure to any hepatotoxic or cardiotoxic agent could be found in any of the three, but the sister may have had infectious hepatitis. The latter two patients had substantial evidence of serious cardiac disease and there is the suspicion that the first patient had a similar problem but proof is lacking.

Efforts have been made to study other members of the family. The parents, who are now fifty-nine and sixty-three years of age, deny similar illnesses in any of their own siblings. The three patients described were from a family of eleven children. The surviving eight are alive and in good health. There are seven children of these eight siblings. All are well. I examined the parents, two of their living children, and one of the grandchildren. One subject (R. M.), born in 1926, the third of eleven children, although completely asymptomatic, was found to have a grade 2 apical systolic murmur, and non-specific RS-T segment and T wave changes in his electrocardiogram. His heart was not enlarged to percussion but a roentgenogram of the chest could not be obtained. No evidence of cardiac disease was found in the others.

Comments. The patient described in detail herein has some similarities to the cirrhotic women reported on by Bearn, Kunkel and Slater [*4*]. In these cases features not usually seen with Laennec's cirrhosis such as arthritis, obscure episodes of fever, and occasional hormonal disturbances including amenorrhea were noted. Marked improvement followed the administration of cortisone in several patients. In one patient the results of a lupus erythematosus cell test was positive.

Bartholomew et al. [*5*] reported on seven similar patients with chronic hepatic disease and lupus erythematosus tests with positive findings. These authors regard them as cases of disseminated lupus erythematosus with grave hepatic involvement the outstanding feature.

The patient reported on herein presented the following features compatible with disseminated lupus erythematosus: unexplained febrile episodes, acute hemolysis, and cardiac disease in a young woman. The absence of significant joint symptoms, inflammation of other mesenchymal surfaces, abnormal urinary findings, hypergammaglobulinemia, and the lupus erythematosus cell phenomenon are against the diagnosis of disseminated lupus erythematosus. The occurrence of myocarditis in acute infectious hepatitis has been described [*6*]. The unique existence of a chronic smoldering hepatitis and a secondary myocarditis in the same patient seems improbable but cannot be excluded. The fever, the cardiac findings, the elevation of the antistreptolysin O titer, the C-reactive protein content of the blood, the response of the fever to salicylate therapy and the finding of group A hemolytic streptococci in the pharynx suggest a diagnosis of acute rheumatic fever. All of this evidence is non-specific and in an adult without previous attacks and without arthritis such a diagnosis seems unlikely. Moreover, the postmortem finding of normal heart valves and the absence of Aschoff bodies excludes rheumatic fever.

The autopsy finding of tuberculous pneumonitis was unexpected but must be regarded as a terminal event since earlier roentgenograms of the chest gave no evidence of pulmonary disease and neither first nor second strengths of purified protein derivative provoked positive skin reactions. Furthermore, surgical exploration of both abdomen and pericardium several months before death revealed no inflammatory process.

The difficulties are apparent in determining whether certain disturbances are produced by the liver or by heart disease. Constrictive pericarditis is a notable example of ascites predominating as the sign of fluid retention. The appearance of ascites followed by its remission for several years may occur with constrictive pericarditis [*7*]. Heart disease with or without cardiac cirrhosis often leads to ascites. Cirrhosis of the liver accompanying chronic constrictive pericarditis usually is characterized by varying degrees of portal fibrosis. The diagnosis of portal and unclassified cirrhosis in a few patients who died of constrictive pericarditis may be explained on this basis [*8*]. Essentially the results of liver function tests were observed in the patient reported on herein were normal until the terminal stage of her illness. It seems probable that the portal fibrosis found at autopsy was

the result of chronic passive congestion. In fact, severe, intractable congestive heart failure seems to be the best explanation for the clinical illness of all three patients.

REVIEW OF CASE REPORTS OF FAMILIAL MYOCARDIOPATHY IN THE LITERATURE

Myocardiopathy of unknown cause but with the strong suggestion of a familial predilection has been reported by several British authors during the past ten years. Brigden [*9*] recently reviewed this subject, presenting the data on eight families from the literature and two from his own experience. A total of thirty-two persons were affected. The clinical picture in familial myocardiopathy is the same as in such noncoronary myocardial diseases as myocarditis and primary amyloidosis. The hallmark of the syndrome is the occurrence of more than one case in the same family, other causes of myocardial disease having been excluded.

At a clinicopathologic conference in 1942 Graybiel [*10*] discussed a young man with anasarca who died with idiopathic cardiac failure. Two siblings were reported to have similar heart disease. One had hepatomegaly and the other had been tapped twice for ascites. Addarii [*11,12*] in 1947 reported on the occurrence of idiopathic cardiac failure in a mother and her two sons. Identical electrocardiograms interpreted as bilateral bundle branch block were recorded in the two sons. The first English publication to call attention to familial myocardial disease was that of Evans [*2*] who in 1949 reported on two families with a total of five patients. He called the disease "familial cardiomegaly." Davies [*13*] described a family of nine children in 1952 of whom five had idiopathic myocardial disease. A child of one of these patients also had evidence of similar disease. Three of these patients died suddenly. Autopsies were performed on two patients. A degree of subaortic stenosis was described in one of the patients at autopsy and an indirect and undetailed report of the other ascribed death to aortic stenosis. The clinical picture in neither was compatible with classic aortic or subaortic stenosis, and the detailed case report revealed marked myocardial fibrosis. The author concluded that a primary disorder of cardiac muscle must be present. A somewhat similar situation was recently reported by Bercu et al. [*22*]. Two brothers had clinical evidence of aortic stenosis and cardiomegaly and a third was said to have cardiomegaly. At autopsy marked hypertrophy of the myocardium and a normal aortic valve was found. The possibility of outflow tract obstruction due to muscle hypertrophy was suggested. A paucity of histologic change and the absence of ventricular dilatation caused the authors not to regard these patients as having the same disorder as that described by Evans [*2*].

Blanshard [*14*] in 1953 reported extensive fibrosis in a heart in a twenty year old man dying of idiopathic myocardial disease. Nine members of the family had premature sudden death. Although Blanshard did not believe that the familial nature should be stressed since the pathologic findings were inflammatory rather than degenerative, Campbell [*15*] in 1956 included the case with others having a familial association of heart disease and suggested that more attention be paid to the strikingly similar clinical pictures and close family connections.

Paulley et al. [*16,17*] reported on three families in which idiopathic cardiac failure occurred in two or more members. He performed complement fixation and dye tests for toxoplasmosis and found positive titers in all. Neither the organisms nor pseudocysts were found in the heart tissues examined, and the antibody titers were low in all but one. Gaunt and Lecutier [*18*] reported on three patients with familial myocardiopathy in whom results of serologic tests for toxoplasmosis were negative. They contend that toxoplasmosis is an unlikely etiologic factor in familial, idiopathic heart disease because: (1) this infection usually is protean in its manifestations; (2) the organism is usually visible on hematoxylin and eosin stained sections of heart muscle of proved cases; and (3) the serologic titers in the proved cases are much higher than in the cases in question.

The only report of this condition encountered in the American literature is that of Sommers [*3*]. He presented the case histories and autopsy findings of three siblings who died of idiopathic cardiac failure at ages twenty-three, twenty-five and twenty-six, respectively. The last death occurred in 1940. Undoubtedly his recollection of patients seen more than fifteen years earlier was stimulated by the recent foreign reports.

Reports of familial heart disease from France [*19*], India [*20*] and Australia [*21*] have appeared recently. The last two have been excluded from Table 1 because of lack of autopsy data in any of the cases. Brigden [*9*] has observed seven addi-

TABLE I

FAMILIAL MYOCARDIOPATHY

Report	Patient	Age and Sex (yr.)	Main Symptoms and Signs	Size of Heart	Electrocardiographic Findings	Course	Weight of Heart (gm.)	Pathologic Condition of the Heart	Incidental Findings
Graybiel [*10*]	Proband	21,M	Weakness,dyspnea, anasarca, and distended neck veins	Enlarged	Complete heart block	Died 6 months after onset in cardiac failure	600	Enlarged muscle fibers; no inflammation	...
	Sister	Early 20's,F	Weakness, dyspnea, anasarca	Much enlarged	Complete heart block	Died approximately 1 year after onset	...	No autopsy	...
	Brother	Early 20's,M	Dyspnea	Unknown	...	...		...	Liver enlarged at appendectomy
Addarii [*11,12*]	Proband	29,M	Syncope, dyspnea on exertion, tachycardia; finally bradycardia	Enlarged	Various arrhythmias and much prolonged QRS	Symptoms began at age 14; died of intractable cardiac failure	900	Scattered scarring throughout and distinct interruption of conducting system	Liver enlarged, hard and lobulated
	Brother	30 ±,M	Exertional dyspnea at age 14, unable to work after age 16; had ascites, cyanosis but little edema	Enlarged	Same as proband	Progressive		...	...
	Mother	34,F	Syncope, intractable heart failure	...	...	Died in heart failure		...	Patient not examined by author
Evans [*2*]	Proband	18,M	Rejected for military service for asymptomatic cardiac enlargement	To anterior axillary line	Left bundle branch block; frequent premature beats	Paroxysmal tachycardia developed, pulmonary edema, died in 5 days	1,134	Dense patchy fibrosis and hypertrophy of individual muscle fibers	...
	Brother	20,M	Giddiness only symptom; rejected for military service because of enlarged heart	Near anterior axillary line	Atrial fibrillation and flutter; also left bundle branch block ?	Living at time of report	...	...	...
	Mother*	43,F	Severe syncopal attacks over 12-year period	Enlarged	Atrial fibrillation and premature beats	Living at time of report	...	...	...
	Proband	12,M	Syncopal episodes similar to epilepsy	Slightly enlarged	First degree A-V block and bundle branch block	Died suddenly 4 years after onset	...	Great hypertrophy of myocardial fibers of left ventricle with much interstitial fibrosis	...
	Mother	42,F	Attacks of tachycardia with syncope	Apical impulse in anterior axillary line	...	Living at time of report	...	...	...
Davies [*13*]	Proband	40,F	Exertional dyspnea 6 years; paroxysmal t achycardia	Apical impulse 9 cm. from mid-sternal line	Nodal rhythm and left ventricular hypertrophy	Living at time of report		...	...
	Sister	38,F	"Nervous debility" and tachycardia few weeks before death	...	...	Collapsed while walking and died immediately	340	Left ventricle dilated; marked generalized fibrosis, minimal subaortic stenosis	...
	Sister	29,F	Palpitation one week before death; previously well	...	...	Sudden unexpected death	440	Left ventricle hypertrophied; "death from syncope due to aortic stenosis"	Autopsy report from police surgeon; no details available and no histologic data
	Sister	16,F	No observations reported	...	...	Sudden death following injection for asthma	...	No autopsy	...
	Brother	27,M	No symptoms	Apex 12 cm. from mid-sternal line	Runs of nodal rhythm, varying ventricular conduction patterns	Living at time of report	...	...	...
	Son	6,M	Irregular heart beat	Normal	Runs of nodal rhythm with normal QRS pattern	Living at time of report	...	...	...
Blanshard [*14*]†	Proband	23,M	Giddiness, syncope, palpitation, and chest pain on exertion	Great enlargement	Non-specific segment and T wave changes; finally left bundle branch block	Duration 4 years; death in cardiac failure	820	Patchy fibrosis, hypertrophy of intact muscle fibers, infiltrates of monocytes and lymphocytes	...
Paulley et al. [*16,17*]	Proband	24,M	Hemiplegia; mental confusion, fever, sudden death	Large	Atrial fibrillation and left bundle branch block	Death 3 months after hospital admission	960	Hypertrophied muscle fibers, generalized fine interstitial fibrosis	Cystic lesions of brain suspicious for toxoplasmosis
	Mother	39,F	Sudden death	...	...	...	550	Fibrotic left ventricle	...
	Brother	16,M	Sudden death	...				No autopsy	...
	Sister	20,F	Cardiac failure during pregnancy	...	Left bundle branch block	Cardiac failure terminating in aortic saddle embolus in few weeks	...	Diffuse fibrosis and nonspecific chronic inflammation	A twin brother was well on examination
	Proband	39,M	Dyspnea, ankle edema for 8 years; chest pain on exertion	Enlarged	Atrial fibrillation and low voltage	Alive at time of report	...	...	Jaundice at age 17

TABLE 1 (*Continued*)

FAMILIAL MYOCARDIOPATHY

Report	Patient	Age and Sex (yr.)	Main Symptoms and Signs	Size of Heart	Electrocardiographic Findings	Course	Weight of Heart (gm.)	Pathologic Condition of the Heart	Incidental Findings
	Brother	23,M	"Sweating on exertion," otherwise asymptomatic	Enlarged	Atrial fibrillation	Alive at time of report	...	...	...
	Brother	43,M	Nocturnal cough and frothy sputum, exertional dyspnea; gallop rhythm	...	Right bundle branch block and atrial fibrillation	Died with aortic saddle embolus in a few months	520	Extensive interstitial fibrosis muscle fibers hypertrophied	...
	Mother	36,F	...			Died 1 year after onset of dropsy	...	No active inflammation	...
Campbell and Turner-Warwick [15]‡	Proband	23,M	Reported by Blanshard (See above)	...	...				
	Mother	29,F	Sudden onset of dyspnea and frank cardiac failure 1 year before death	Large globular	Left bundle branch block; (QRS = 0.22 sec.)	Responded well to treatment but suddenly died 1 year after admission	...	No autopsy	...
	Proband	36,M	Syncopal attacks associated with bradycardia	Danzer ratio 0.55	Sinus bradycardia; A-V block intermittently	Death in syncopal attack 3 months after onset	...	Hypertrophy of myocardial fibers; some showed central clear spaces; no fibrosis	Jaundice at age 17 without sequellae
	Mother§	66,F	Syncopal attacks from age 26. Blood pressure 104/80 mm. Hg at age 60; at age 66 220/110 mm. Hg	Danzer ratio 0.53 in 1928 became larger later	Sinus bradycardia with paroxysms of atrial tachycardia; also showed shortened P-R interval with prolonged QRS	Alive at time of report	...	...	...
Gaunt and Lecutier [18]	Proband	49,M	Dyspnea, Stokes-Adams attacks	Gross enlargement	Auricular flutter; A-V dissociation, greatly increased amplitude of all complexes	Died in Stokes-Adams attack 2 years after onset	737	Hypertrophy of all chambers; multiple vacuoles in the myocardial fibers; hypertrophy of individual muscle fibers; patchy fibrosis	...
	Maternal niece	23,F	Slight dyspnea on exertion; previously had migratory arthralgia but erythrocyte sedimentation rate normal	Gross cardiomegaly	Greatly increased amplitude of QRS deflections and T waves and change in RS-T segments	Lost to follow up	...	...	...
	Sister	53,F	Stokes-Adams attacks; dyspnea for 3 years	Considerable enlargement	Increase in amplitude of QRS deflections; changes in RS-T segments and T-waves	Subsequently died at home	...	No autopsy	...
Sommers [3]	Proband	23,F	Abdominal pain, vomiting and slight fever, followed by dyspnea 1 week before admission	Not stated	Varying changes in QRS and T waves	Died of cardiac failure and pulmonary embolism 1 month after onset	400	Mural thrombosis; marked dilatation of all chambers; microscopically normal except for swelling and edema in a few areas	...
	Brother	26,M	Dyspnea, low grade fever, hemoptysis and chest pain	Enlarged	Not reported	Died in cardiac failure 2 months after onset	520	Mural thrombi; widespread scarring throughout myocardium; scattered groups of lymphocytes and neutrophils	Jaundice, anasarca, pulmonary infarcts, complete situs inversus
	Brother	25,M	Dyspnea progressing to frank cardiac failure	Danzer ratio 0.496	Dextrocardia; notching of QRS in leads I, II, III; T wave changes	Death 5 months after onset of symptoms in cardiac failure	560	Mural thrombi; great dilatation; microscopically normal except for 2 fields which showed acute myocarditis	...
Soulie et al. [19]	Proband‖	22,M	Cardiomegaly discovered at age 17; cardiac failure at age 21; hemiplegia 5 months before death	Huge globular heart	Atrial fibrillation and left bundle branch block	Digitalis, diuretics, ineffective; died suddenly during bout of tachycardia	750	Scattered fibrosis and groups of round cells; hypertrophy with vacuolization of a number of muscle fibers	...
	Sister	13,F	No symptoms	Enlarged	Left ventricular hypertrophy	Increasing cardiomegaly. Living at time of report	...	...	...
	Maternal Uncle	54,M	Hemiplegia at age 52; cardiac enlargement and cardiac failure discovered at that time; blood pressure 170/110 mm. Hg	Large by x-ray film	Left ventricular hypertrophy	Initial improvement but recurrence of cardiac failure and sudden death 3 years after onset	...	...	...

* Three siblings of this forty-three year old mother died suddenly and unexpectedly at twenty-one, twenty-six and thirty years of age.
† Other affected members of family listed under Campbell and Turner-Warwick.
‡ Blanshard [14] stated that eight of twelve siblings of this patient died of heart disease, four between twenty-three and forty years of age and four in infancy. An aunt was also said to have died suddenly.
§ Several members of earlier generations on the mother's side were believed to have died of heart disease at early ages.
‖ A brother died suddenly at the age of twenty after a football game. No details of case are known.

tional patients occurring in two families; these are not shown in Table 1.

COMMENTS

Table 1 records the brief abstracts from the literature of thirty-eight patients with heart disease of unknown cause. There is evidence in each instance of similar disease in one or more members of the family. None of the patients at autopsy (Table 1) had valvular heart disease or Aschoff bodies, nor was there any evidence of occlusive coronary artery disease, although a few of the older patients had atheromata. The vascular supply to the myocardium was regarded as unequivocally adequate in all patients. One patient [*15*] had a diastolic blood pressure of 110 mm. Hg, but the cardiac findings preceded the hypertension. No other patient had hypertension.

Certain other similarities may be pointed out, in addition to the basic criteria that they be familial and idiopathic, which more or less segregate them from patients with other kinds of heart disease.

The symptoms are as follows: dyspnea on exertion, as expected, was the most common presenting symptom. Many complained of palpitation, both spontaneous and exertional. This is accounted for by the frequent and variable arrhythmias revealed by the electrocardiograms. Syncope was the next most common symptom. Sensations of giddiness and lethargy often proceeding to frank syncope were reported several times. Stokes-Adams attacks were the principal presenting complaints in two. Chest pain on exertion occurred in two instances. Reference is made to several presumably asymptomatic relatives of these patients, who died suddenly [*2*].

The following signs are observed: cardiomegaly was seen in every patient in Table 1, except for two, observed early in their illness. Distention of the neck veins was observed in several, and severe dependent edema with ascites was noted. A triple rhythm was heard more often than not. This sign, coupled with distended neck veins and a congested liver in a young patient, suggests the diagnosis of constrictive pericarditis. Brigden [*9*] in discussing the non-coronary myocardiopathies points out that the third heart sound is not so early nor so sharp as the protodiastolic sound in constrictive pericarditis.

The electrocardiographic tests revealed the following: the variety of findings in both the atrial and ventricular complexes indicates a diffuse process. Arrhythmias included paroxysmal atrial tachycardia, nodal rhythms, atrial flutter, atrial fibrillation and complete heart block. Indeed, these arrhythmias often cause the initial symptoms, syncope from tachycardia or marked bradycardia being common. Diffuse intraventricular conduction defects often resembling left bundle branch block were observed frequently. It is assumed that the several instances of sudden death were caused by cardiac mechanism disturbances.

The course of this disease is as follows: the mean duration of life in the fatal cases was one year after the onset of symptoms. The majority progressed to intractable congestive heart failure which led to death.

The pathologic findings are as follows: The conspicuous cardiomegaly in this condition led Evans [*2*] to apply the name familial cardiomegaly. Heart weights from 270 to 1,134 gm. were noted in the patients at autopsy. The average was 658 gm. Scattered fibrosis was the most frequently listed histologic finding in the myocardium. The majority of the patients also had hypertrophy of individual muscle fibers and central vacuolization. Infiltration with round cells was recorded in a few instances. The microscopic findings were not specific in any case. A variety of lesions were observed, some inflammatory, some purely degenerative and others a mixture of both. No clinicopathologic correlation was seen. This lack of consistency in the microscopic findings is the most damaging criticism of the thesis that familial myocardiopathy is a distinct entity.

Hereditary considerations are as follows: the familial aggregation of these patients is striking. Whether there is an unidentified and unsuspected injurious agent such as infection, toxic substance or nutritional deficiency, cannot be said. The possibility of cardiac involvement with toxoplasmosis or with chronic Chagas' disease has been mentioned [*16*]. The evidence against all these factors is circumstantial. The arguments are based on the exclusion of all known causative factors. The various injurious agents capable of affecting the heart do not in general single out the heart but cause disturbances throughout the body so that the myocardial disorders are apt to be among the least apparent.

Although the evidence is somewhat scant, a genetic basis for the familial aggregation of this

condition seems acceptable. Campbell and Turner-Warwick [*15*] have stated that inheritance as a Mendelian dominant is probable. It may be noted from Table 1 that the existence of the condition in two generations indicates transmission by the mother, never the father.

Evans [*2*] has suggested that the condition may be analogous to Friedreich's ataxia and the hereditary myopathies presenting a variety of histologic pictures. None of the patients in Table 1 showed primary neurologic or muscular abnormalities.

SUMMARY

The occurrence of remarkably similar cardiac disease of unknown etiology in two siblings and a history of identical symptoms leading to the death of a third, called attention to familial cardiomegaly, an entity described by Evans [*2*] in 1949. This disease should be suspected along with the other non-coronary myocardial myopathies when evidence for the common varieties of heart disease is lacking. Neither clinical nor pathological observations serve to differentiate it from so-called "cardiac hypertrophy of unknown etiology" [*1*].

That there is a familial myocardial disease seems very probable; that it is genetically transmitted is uncertain but seems probable. Resolution of the problems raised may come from careful study and reporting of additional cases.

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Reviews

Mechanisms of Salt and Water Retention in Congestive Heart Failure*

The Importance of Aldosterone

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THE sequence of events between the primary myocardial defect in congestive heart failure and the formation of peripheral edema or ascites has for years been an intriguing problem for discussion. The thesis that venous hypertension and the associated engorgement of the systemic veins is primarily responsible for cardiac edema long held sway, and was championed by Harrison [*1*] under the designation of "backward failure." It was contended that elevated venous pressure leads to increased capillary pressure, augmented filtration, and edema. Numerous secondary factors contributing to the accumulation of tissue fluid were recognized [*2*].

In 1944 to 1946 a new era in our knowledge of the physiology of congestive heart failure was ushered in by the work of Warren, Stead, Merrill and associates [*3–5*]. They elaborated upon the "forward failure" hypothesis, emphasized the role of the kidney in the formation of edema, and pointed out the importance of a low rate of glomerular filtration (GFR) in the sodium retention of congestive failure. The details of the "forward failure" theory, as modified and presented by this group of workers, have been described repeatedly in previous reviews [*2,6–11*]. Merrill's finding [*5*] of a low GFR and renal plasma flow (RPF) in heart failure was soon confirmed by Mokotoff, Ross and Leiter [*12*].

The principal views held in recent years are presented in Figure 1. According to the "forward failure" concept, the retention of Na by the kidney is primarily the result of some alteration in renal hemodynamic functions [*13*]. It is generally agreed that the reduced renal function is secondary to decreased cardiac output. Others [*14–19*] support the view that an increase in circulating adrenocortical sodium retaining hormone, which is now known to be aldosterone, with its direct effect upon the renal tubular transport of Na constitutes a primary mechanism in the renal retention of salt and water. The purpose of this review is to present the recent evidence on mechanisms of salt and water retention in congestive heart failure, with particular emphasis on the role of aldosterone. The difficulties in elucidating these mechanisms in man have been almost insurmountable [*20*] and have led to studies in experimental animals.

Experimental Cardiac Failure in the Dog. Dogs with experimental congestive heart failure provide many advantages over man for the study of the pathogenesis of cardiac failure. A suitable control period of observations can be obtained. The early stages of heart failure during which the pathogenic changes are most clearly defined can be more readily studied than in man. Superimposed long-term metabolic factors and the effects of numerous therapeutic agents are not present to obscure alterations important in the pathogenesis of heart failure. Drastic experimental manipulations or surgical procedures such as bilateral adrenalectomy and total hypophysectomy can be performed and evaluated more easily than in man. For these and many other reasons extensive studies have been made in the experimental animal, especially the dog. In many instances the parallelism between the findings in man and dog is striking and studies of experimental heart failure have

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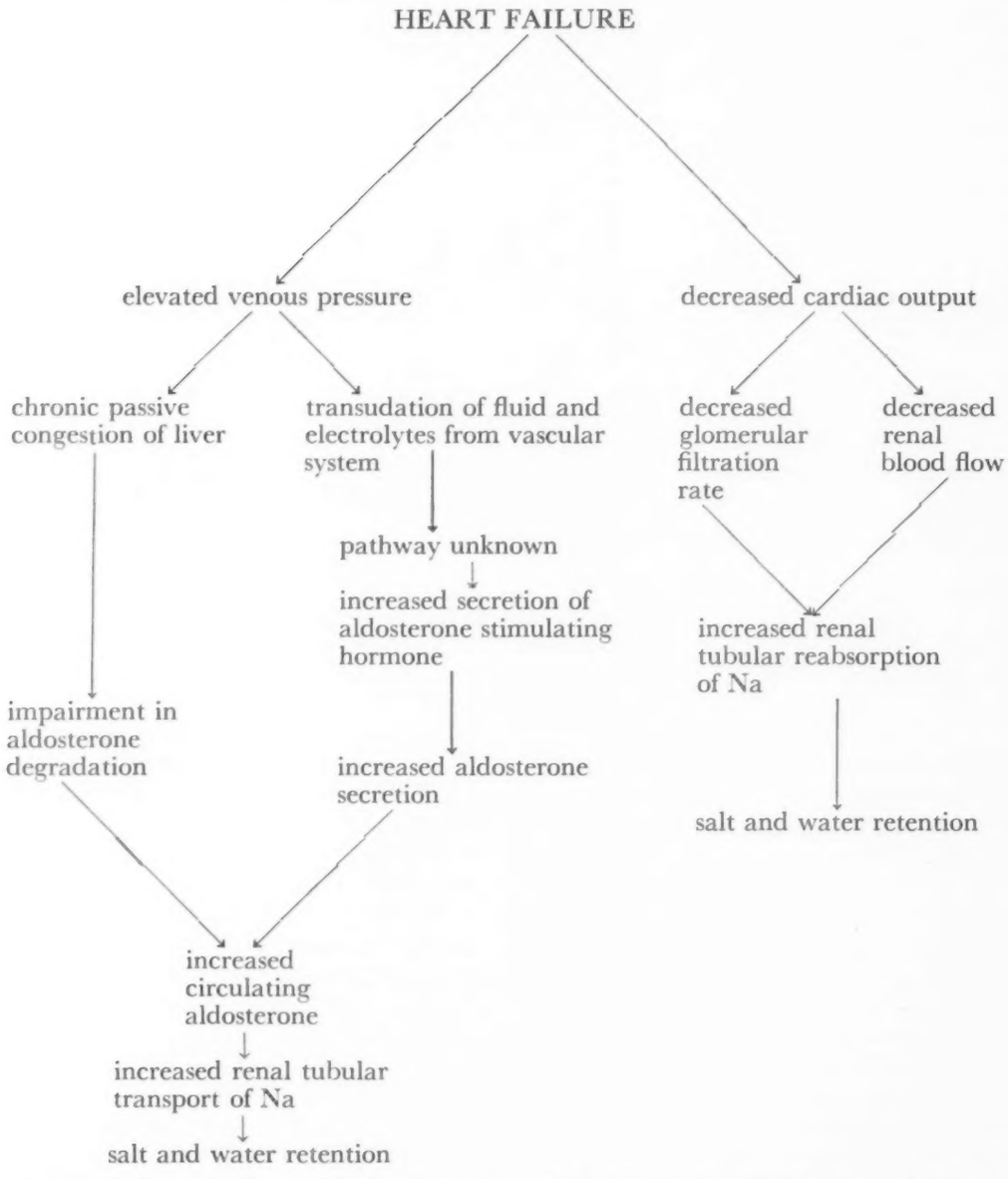


FIG. 1. Possible pathways leading to the retention of salt and water in congestive heart failure.

provided many new facts to help elucidate the physiology of congestive failure in man.

The first satisfactory experimental preparation for the study of congestive failure was developed in 1950 by Barger, Richardson and Roe [*21,22*]. After extensive evaluation of a number of valvular lesions, they found that in dogs with tricuspid insufficiency and pulmonic stenosis a syndrome developed almost identical with right-sided heart failure in man. The preparation is very easy to produce if the technic of controlled progressive stenosis which was developed by Ellison and Major [*23*] is applied to the pulmonary artery [*24*]. Davis, Hyatt and Howell [*25*] produced experimental cardiac failure in dogs by controlled progressive pulmonic stenosis. These animals show marked changes in cardiovascular function and either die of cardiac failure within a few weeks or cardiac compensation occurs and a diuresis ensues. Dogs with experimental ascites secondary to thoracic inferior vena cava constriction,* a method which was first described by Bolton [*26*] in 1907,

* These animals resemble very closely patients with decompensated hepatic cirrhosis as regards the metabolism of salt and water.

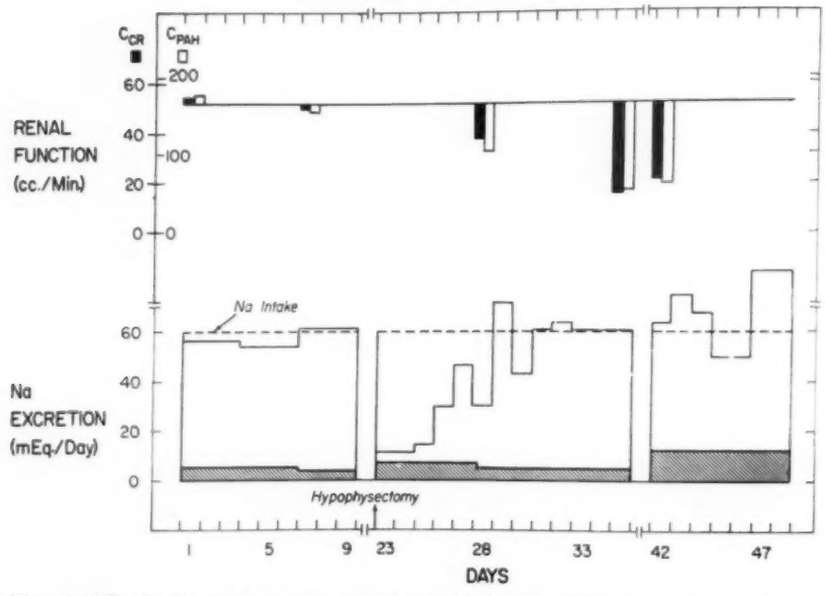


FIG. 2. Effects of hypophysectomy on the renal clearances of creatinine (C_{CR}) and paraa-minohippurate (C_{PAH}) and on Na excretion in the dog. The hatched area indicates fecal Na excretion, the open area above it urinary Na excretion.

provide a better experimental situation than dogs with heart failure for the study of salt and water metabolism and secondary hyperaldosteronism. These animals have been studied extensively [*17,19,26–31*] and the mechanisms of salt and water retention appear to be similar if not identical to those in experimental heart failure [*17,19,22,25,32,33*].

The Role of a Low Glomerular Filtration Rate and a High Filtration Fraction. The importance of a low rate of glomerular filtration in the retention of salt and water in congestive heart failure has been recognized for more than a decade. It has been repeatedly demonstrated that an acute decrease in GFR results in decreased excretion of Na and water. The most extensive data have been obtained from studies in the dog [*34–38*] but observations in man [*39,40*] are sufficient to establish this relationship. Data on the duration of the effect of sudden decrease in GFR on Na excretion are meager but an indication of the time required for homeostatic adjustment and Na balance has been provided from studies of hypophysectomized dogs. Following hypophysectomy a drop in GFR and RPF occurs within the first few days (no measurements are available during the first few hours) and renal function reaches a level, within 6 weeks, of 20 to 35 per cent of normal [*41,42*]. During the first four to five days after hypophysectomy, Na retention occurs but Na balance is soon achieved. (Fig. 2.) Since aldosterone secretion is decreased after hypophysectomy [*43,44*] the drop in GFR seems to be the most likely explanation for the Na retention. Sodium balance is achieved by homeostatic mechanisms despite a persistently low GFR [*45*]. In man, it seems clear that a rapid fall in GFR associated with the onset of cardiac decompensation or the rapid development of more severe cardiac decompensation in patients with chronic heart failure may promote the retention of salt and water.

It has been demonstrated repeatedly [*46–49*] that the GFR is frequently within normal limits in patients with chronic congestive heart failure and that cardiac compensation may occur with no change in GFR [*46*]. Similar findings [*8,15,25,32,50,51*] have been obtained in dogs with congestive failure in which each dog served as its own control. The GFR in the postabsorptive state is frequently within normal limits in dogs with experimental low output failure. In dogs with high output failure secondary to anemia [*51*], the GFR and RPF in the postabsorptive state were frequently elevated. As in man, sudden declines in renal function undoubtedly contribute to Na retention in dogs with experimental heart failure.

Most studies in experimental animals and man have been limited to evaluation of postabsorptive renal function. Since a rise in GFR and RPF occurs after a meal and, in the dog,

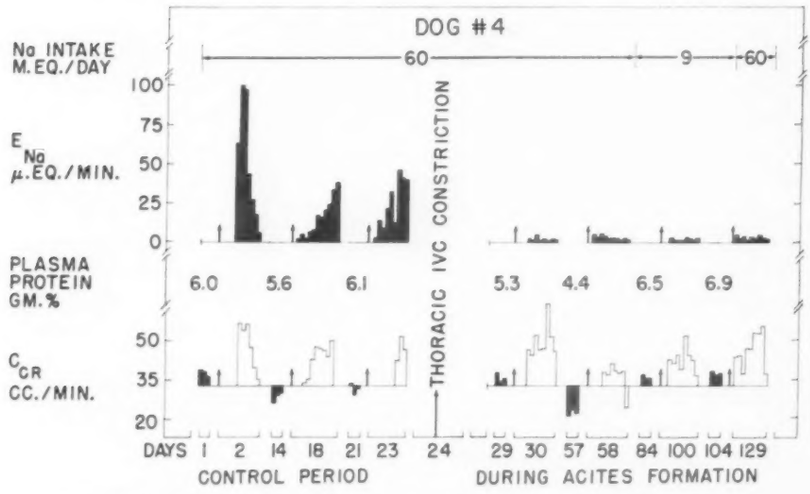


FIG. 3. Relation of postabsorptive (solid black area) and postprandial (open area) glomerular filtration rate (C_{CR}) to the renal excretion of Na (E_{Na}) before and after constriction of the thoracic inferior vena cava. The horizontal base line for C_{CR} represents the average value for the nine postabsorptive values obtained before caval constriction. Hourly measurements were made of postprandial C_{CR} and Na excretion. Vertical arrows show the time of food ingestion. (From: DAVIS, J. O. and HOWELL, D. S., *Circulation Res.*, 1: 171, 1953 [*30*].)

this increase is associated with excretion of the major portion of the dietary electrolyte intake, complete evaluation of the role of GFR has necessitated measurement of postprandial renal function. Observations [*30*] showed that both postabsorptive GFR and the increase in GFR after a meal were frequently the same in normal dogs in Na balance as after caval constriction and during almost complete Na retention. (Fig. 3.) These data and those of Barger [*8*] on Na retention during unilateral, renal intra-arterial infusion of salt to dogs with heart failure provide convincing evidence that an alteration in the renal tubular transport of Na is present in congestive heart failure.

The importance of baroreceptors in the regulation of Na excretion was suggested by O'Connor in 1955 [*52*]. He occluded the common carotid arteries and observed an increase in renal Na excretion which was associated with a rise in arterial pressure. The natriuresis may have resulted from an increase in GFR.

The possibility that baroreceptors may respond to alterations in the volume of body fluid and that Na retention may be part of the moderator reflex has also been supported by Barger [*8,53*]. In this event, the carotid sinus and aortic depressor nerves would constitute the afferent limb of the system. Barger, Liebowitz and Muldowney [*53*] have proposed that cardiac impairment may lead to a decreased rate of firing of the carotid sinus and aortic arch nerves and a reflex increase in sympathetic activity with resultant Na retention. Evidence for the role of the renal nerves was provided by an increase in Na and excretion of water following the renal intra-arterial injection of Dibenzyline® in a dog with congestive failure, whereas less effect was observed in a normal dog. It seems likely that the natriuresis following Dibenzyline was due to increased GFR.

The role of the moderator reflexes and resultant changes in GFR in the regulation of Na excretion has also been indicated by the experiments of Gilmore [*54*], and personal communication. During stellate ganglion stimulation which produced an increase in cardiac output and pulse pressure a striking diuresis and chloruresis occurred. The response was evident within one to two minutes after the onset of stimulation and ceased after a similar period following cessation of stimulation. Measurements of GFR showed similar directional changes. The increase in GFR did not appear to be related solely to an increase in renal arterial pressure since vagotomy diminished GFR and the diuresis while the elevation in arterial pressure was the same or greater.

Although a possible direct influence of the renal nerves on the renal tubular transport of Na cannot be excluded, it seems more likely that the

role of the nerves to the kidney is limited to the regulation of RPF and GFR. It has recently been demonstrated by Carpenter and associates [*55*] that Na retention and the formation of ascites occurred with completely denervated kidney. Carpenter et al. transplanted the left kidney to the neck, removed the right kidney and constricted the thoracic inferior vena cava in dogs. Hyperaldosteronism, marked Na retention and ascites formation occurred. It seems clear, therefore, that the renal nerves are not essential for the renal tubular transport mechanism leading to Na retention in experimental secondary hyperaldosteronism.

Barger [*8*] called attention to the possible importance of a high filtration fraction (FF) in cardiac failure. He pointed out that the increase in postglomerular colloid osmotic pressure and the resultant gradient from the tubular lumen to the peritubular capillary might influence the reabsorption of electrolytes and water by the renal tubule cells. Barger emphasized, however, that Werko et al. [*56*] found a high FF in patients with heart disease long before the appearance of signs of congestive heart failure. The possible role of a high FF has been considered recently by Vander et al. [*57*]. They suggested that water is reabsorbed passively as a consequence of the osmotic gradient created by the elevation of FF and the associated increase in postglomerular oncotic pressure; according to their hypothesis Na reabsorption occurs passively secondary to absorption of water. Attention was called to the many instances of Na retention in the presence of a high FF.

Evidence may be cited against the hypothesis that a high FF constitutes a mechanism for the chronic retention of Na in heart failure. First, in experimental cardiac failure of the high output type [*51*] the FF decreased in four of five dogs, either at the onset of or during marked Na retention. Before the appearance of Na retention, the FF was elevated in comparison with normal values for FF. Also as Barger pointed out, Werko et al. [*56*] reported a high FF in patients with heart disease long before signs of frank congestive failure appeared and, consequently, in the absence of Na retention. Fishman and co-workers [*58*] found a high FF in patients with cor pulmonale in the presence of cardiac failure. It is well known that patients with hypertensive disease may have a high FF in the absence of cardiac failure. In acute experimental pericarditis with Na retention and ascites [*15*] the FF was unchanged or reduced. Secondly, in dogs with ascites secondary to partial ligation of the thoracic inferior vena cava [*30*], the postglomerular colloid osmotic pressure was markedly reduced in comparison with the level of pressure during the control period. For example, a normal dog with a FF of 33 per cent and a calculated plasma colloid osmotic pressure of 25 mm. Hg showed a rise in FF to 42 per cent following caval constriction but the colloid osmotic pressure fell to 12 mm. Hg as a result of protein depletion [*30*]. Calculations of postglomerular oncotic pressure show a decrease from 37 to 21 mm. Hg which occurred in association with the appearance of marked Na retention.

Increased Circulating Aldosterone. Evidence for the presence of hyperaldosteronemia and for its important pathogenic role in congestive heart failure is now conclusive. As early as 1941 Raab [*59*] reported that the blood level of adrenocortical hormones was elevated in cardiac decompensation. During the next few years there was considerable interest in renal hemodynamic function and little attention was given to the role of the adrenal cortex. In 1950, however, Deming and Luetscher [*60*] reported that urine from patients with congestive heart failure showed increased sodium-retaining activity.

Strong indirect evidence for the importance of the adrenal cortex in the pathogenesis of cardiac failure was provided by studies of electrolytes in sweat, saliva, urine and feces. In patients with congestive failure and decompensated hepatic cirrhosis, the concentration of Na was found to be reduced in feces [*61*], sweat [*61–63*] and saliva [*61,63,64*]. Also, in dogs with experimental ascites the fecal excretion of Na was strikingly decreased, whereas fecal K output was markedly elevated [*30*]. The ratio of fecal Na to fecal K excretion ranged from 2.2 to 5.5 for normal dogs compared with 0.1 to 0.4 for dogs with ascites and intact adrenals. (Fig. 4.) Dennis and Wood [*64*] demonstrated that adrenocortical sodium-retaining hormones influence the intestinal mucosal transport of Na and K, and the data from fecal electrolyte studies indicate the presence of an increase in circulating sodium-retaining hormone from the adrenal cortex. This was confirmed by removing the adrenal glands in dogs with chronic ascites. (Fig. 4.) Following unilateral adrenalectomy fecal Na/K excretion increased in 5 of 7 dogs with thoracic caval constriction and ascites

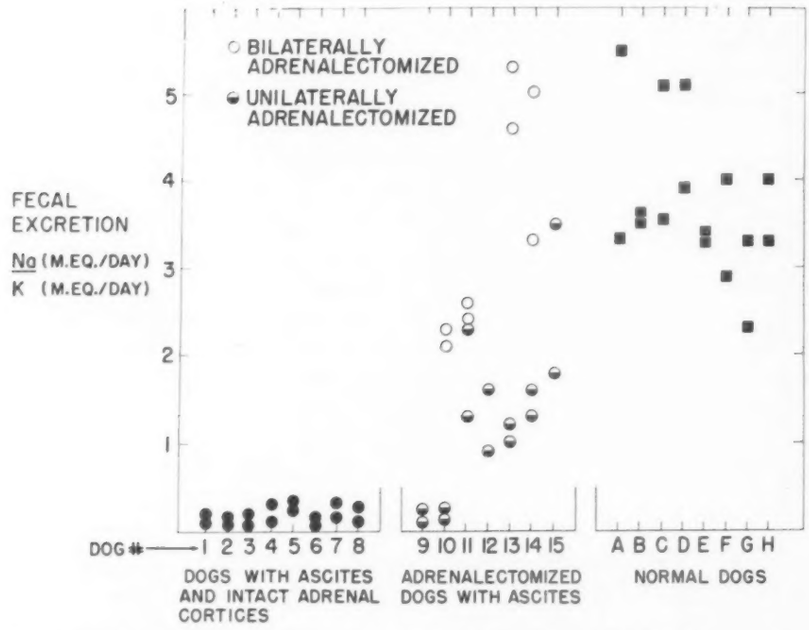


FIG. 4. Effects of unilateral and bilateral adrenalectomy on fecal Na/K excretion. Following bilateral adrenalectomy, 3 mg./day of DCA were given. The sodium and potassium intake was 30 and 18 mEq./day, respectively.

(no supportive therapy); in the other two animals, the low ratio of fecal Na/K excretion was present. After bilateral adrenalectomy and during maintenance on 3 mg./day of desoxycorticosterone acetate (DCA) a further increase in fecal Na/K excretion occurred. More recently, data have become available on the inverse relationship of aldosterone excretion in urine to fecal Na/K output. Duncan, Liddle and Bartter [*66*] reported increased urinary aldosterone excretion, decreased fecal Na and increased fecal K output for normal men during Na depletion and for patients with congestive failure; the studies were made during ingestion of a cation exchange resin. This same relationship of aldosterone output in urine to fecal Na/K excretion has been found in dogs with experimental ascites [*67*].

There were additional reports that increased sodium-retaining activity is present in urine of patients with cardiac failure [*18,68*], cirrhosis of the liver [*18,69*], and nephrosis [*18,70*]. Following the isolation and crystallization of aldosterone in 1952 the presence of increased amounts of aldosterone in urine was demonstrated in studies of patients [*71*] and of dogs [*72*] with edema or ascites. The data in both man and dog show that the blood level of aldosterone is elevated in clinical and experimental states with edema or ascites.

Hypersecretion of Aldosterone. The high level of circulating aldosterone could be the result of hypersecretion of aldosterone by the adrenal cortex, a decreased rate of inactivation of aldosterone, or both. Increased secretion of aldosterone in the blood of the adrenal veins was demonstrated [*19*] in dogs with chronic caval constriction and in dogs with experimental cardiac failure of several days' to several weeks' duration. Hypersecretion of aldosterone has been reported in nephrotic rats with edema and ascites by Singer [*73*]. More recently, the earlier finding of increased aldosterone secretion in dogs with chronic thoracic inferior vena cava constriction and ascites has been confirmed [*74*] by using the double isotope derivative technic of Kliman and Peterson [*75*]. (Fig. 5.) Indirect evidence for hypersecretion of hormones from the zona glomerulosa of the adrenal cortex has been provided by Hamilton, Brown and Hague [*76*] for dogs with experimental ascites and by Deane and Barger [*77*] for dogs with experimental congestive failure. The failure of Driscol et al. [*78*] to find increased secretion of aldosterone in dogs with controlled progressive pulmonic stenosis is probably a reflection of the absence of cardiac failure in their preparations. We have not observed experimental congestive failure with Na retention and ascites in the presence of venous pressures as low as Driscol et al.

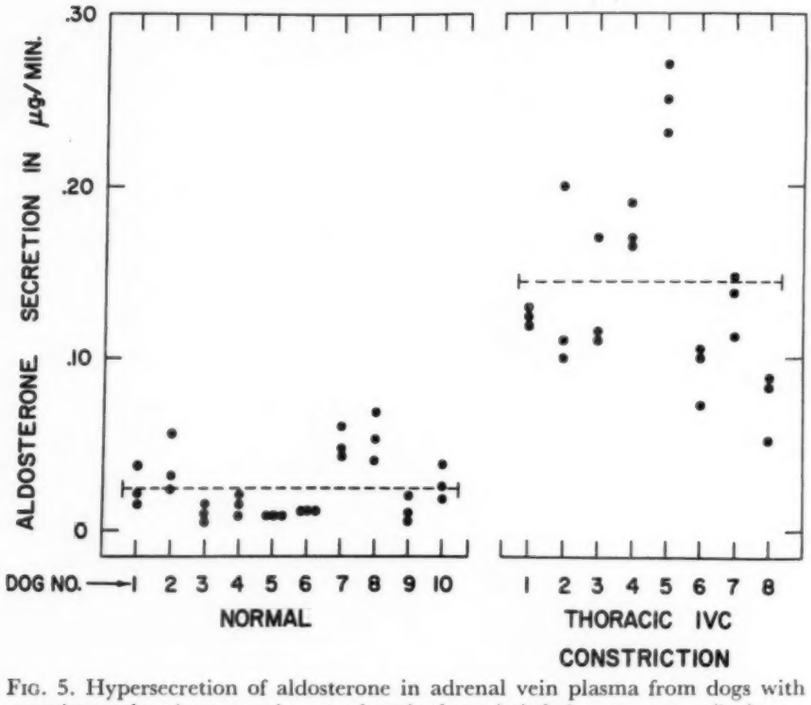


FIG. 5. Hypersecretion of aldosterone in adrenal vein plasma from dogs with experimental ascites secondary to chronic thoracic inferior vena cava (ivc) constriction. The three determinations were made at thirty minute intervals in dogs under Nembutal® anesthesia. (From: YANKOPOULOS, N. A. et al., *J. Clin. Invest.*, 38: 1278, 1959 [*74*].)

reported. It seems likely that cardiac compensation had occurred in their animals before studies of aldosterone secretion were made; no measurements of Na excretion were reported.

Studies of aldosterone secretion in man were first made by Ayres and associates [*79*]. They applied the isotope dilution technic for measurement of aldosterone production and found values of 170 to 190 μg./day for normal man. Similar rates of secretion (150 to 300 μg./day) have been reported for normal subjects on unselected diets by Ulick, Laragh and Lieberman [*80*]. These workers injected labeled aldosterone and measured the specific activity of a urinary metabolite of aldosterone. With this technic, secretion rates for a patient with hepatic cirrhosis and ascites and for a patient with the nephrotic syndrome were found to be 1,570 to 2,080 and 6,600 μg./day, respectively. Similar results have been obtained by Peterson [*81*] who used the turnover rate of tritiated aldosterone to measure the rate of aldosterone secretion. A patient with decompensated hepatic cirrhosis and ascites secreted 3,000 μg./day in contrast to a secretion rate of 560 μg./day for a normal subject; Na intake was 200 mg./day in both cases. Normal rates of aldosterone secretion have been reported for patients with heart failure by Ulick and coworkers [*80*]. They found secretion rates of 300 and 470 μg./day for two patients with chronic heart failure with edema and ascites. It is not clear why these patients had normal rates of aldosterone secretion since the low Na intake per se should have resulted in hypersecretion of aldosterone [*82*]. More studies are needed to clarify the situation in patients with congestive heart failure but the evidence for hypersecretien in dogs with experimental cardiac failure and in patients with cirrhosis and ascites is now conclusive.

Decreased Rate of Inactivation of Aldosterone by the Congested Liver. The possible importance of the congested liver in contributing to the high blood level of aldosterone in right heart failure has been considered by several workers [*72,83–86*]. Chart et al. [*83*] demonstrated that actively respiring rat liver slices incubated with material containing aldosterone completely inactivated the biological potency of this hormone. Under anaerobic conditions, however, there was impairment of rat liver slices to inactivate aldosterone. This finding suggests the possibility that a congested liver might contribute to the increase in circulating aldosterone in various

clinical syndromes with chronic hepatic congestion and edema or ascites.

Evidence in support of this hypothesis has been presented by Yates and co-workers [*84,85*] from studies of rats with hepatic venous congestion. An enzymatic "lesion" resulting from hepatic venous congestion was described; there was impairment in the enzymatic reduction of ring A of desoxycorticosterone, cortisone, hydrocortisone and aldosterone. DCA-treated rats with hepatic venous congestion showed a significantly greater degree of Na retention than a similarly treated control group of normal subjects; the authors suggested that decreased inactivation of DCA occurred secondary to congestion of the liver. However, as Yates [*84*] pointed out, another interpretation of this finding is that the kidney was more sensitive to DCA in the presence of hepatic venous congestion. Yates and co-workers also reported that the survival of adrenalectomized venous congested rats was markedly prolonged after withdrawal of DCA in comparison with adrenalectomized control rats. This finding was explained on the basis of decreased inactivation of DCA but these workers also mentioned the possibility that retained salt and water contributed to the increased survival time.

More recently, Ayers et al. [*86*] have studied the disappearance of tritiated aldosterone from plasma in dogs before and after thoracic inferior vena cava constriction. The biological half life ($T_{½}$) of aldosterone was markedly prolonged following caval constriction in five of seven dogs; these five animals had a higher venous pressure than the two animals with an unchanged $T_{½}$ for aldosterone. Following hepatectomy the disappearance curve for aldosterone was almost flat. These observations support the view that chronic hepatic congestion contributes to hyperaldosteronemia, but the more consistent occurrence and marked degree of hypersecretion of aldosterone [*19,74*] indicate that increased production of aldosterone is the primary mechanism responsible for the increased plasma level of this hormone.

Of considerable interest in this connection is the finding of Peterson [*87*] that the rate of disappearance of tritiated aldosterone from the blood of patients with decompensated hepatic cirrhosis was similar to that of normal subjects. The miscible pool and turnover rate of aldosterone were measured in one of their patients with hepatic cirrhosis and the rate of aldosterone secretion was markedly increased. These findings also indicate that increased secretion rather than a decreased rate of metabolism of aldosterone is the primary mechanism responsible for hyperaldosteronemia.

Relation of Increased Circulating Aldosterone to Renal Electrolyte Excretion. The importance of hyperaldosteronemia in the renal retention of Na has become increasingly evident. Nevertheless, doubt as to the relation of aldosterone to Na retention has been raised by Barger [*8,77*] and by Farrell [*88*]. Before aldosterone was discovered, its physiological prototype, desoxycorticosterone, provided data on the quantitative relation of the amount of sodium-retaining hormone present to the degree of Na retention in adrenalectomized dogs with chronic experimental ascites [*17*]. For maintenance, only 0.5 mg./day of DCA was adequate and Na balance was attained. (Fig. 6.) This amount of DCA is the same quantity required for maintenance of the adrenalectomized dog in Na balance. Potassium balance also was achieved in both adrenalectomized dogs and dogs with partial ligation of the inferior vena cava and ascites during maintenance on 0.5 mg./day of DCA. As the dosage of DCA was increased from 0.5 to 25 mg./day, a progressive reduction in both urinary and fecal Na excretion occurred. The urinary K output declined while fecal K excretion increased. During administration of 3 to 10 mg./day of DCA, which is six to twenty times the minimal maintenance dose, the urinary and fecal pattern of electrolyte excretion was identical with that in dogs with ascites and intact adrenals. This six- to twentyfold increase in the DCA requirement for duplication of electrolyte excretion is similar in magnitude to the sixfold increase in aldosterone secretion. (Fig. 5.) Also, in adrenalectomized dogs with experimental heart failure [*32*] the degree of Na retention increased as the dose of DCA was increased from 1 to 25 mg./day during administration of cortisone to maintain circulatory function. No attempt was made to determine the minimal maintenance dose of DCA during injection of 25 mg./day of cortisone in these adrenalectomized dogs before heart failure was induced because this dose of cortisone alone is quite adequate to maintain the simple adrenalectomized dog [*89*]. It should be emphasized that the effects of DCA and aldosterone on the renal excretion of Na and K by the kidney are qualitatively identical [*90*].

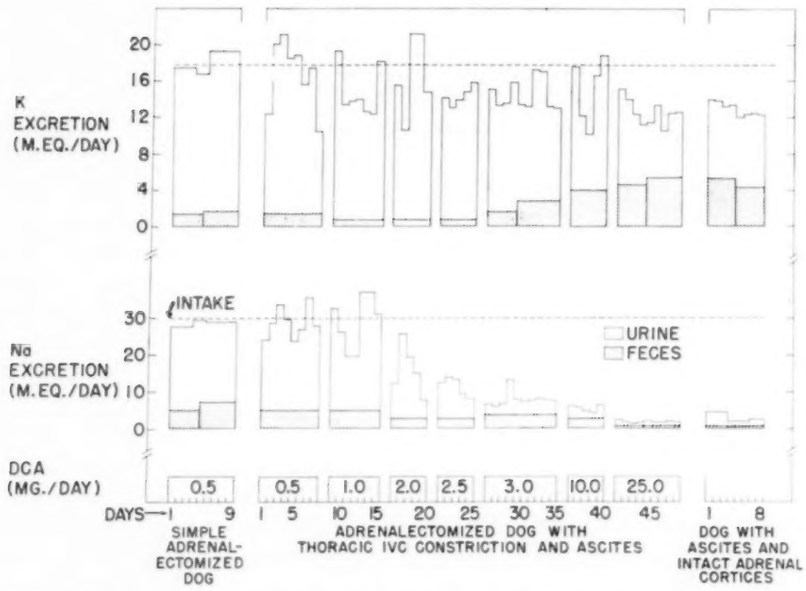


FIG. 6. Effects of various doses of DCA on urinary and fecal Na and K excretion in an adrenalectomized dog with thoracic caval constriction and ascites. For comparison, balance data are also shown for an adrenalectomized dog receiving 0.5 mg./day of DCA, and for a dog with ascites and intact adrenals.

The effects of bilateral adrenalectomy and subsequent therapy with cortisone have also been studied in patients with ascites secondary to cirrhosis of the liver [*91,92*]. Before adrenalectomy the patients showed persistent marked Na retention. Following adrenalectomy and during administration of small doses of cortisone (12.5 mg./day or less) large quantities of salt and water were excreted. This finding indicates the necessity of sodium-retaining activity greater than that provided by 12.5 mg./day of cortisone for the marked Na retention observed before adrenalectomy.

After the increased sodium-retaining material in urine from patients with cardiac edema was identified as aldosterone, several studies [*18,66, 72,93–96*] indicated an inverse correlation between the rate of aldosterone excretion in urine and Na excretion. Luetscher and Johnson [*18*] were first to report this relationship. Later, in dogs with experimental ascites [*72*], hyperaldosteronuria was associated with Na retention whereas in normal dogs in Na balance aldosterone was undetectable in urine. Also, in hypophysectomized dogs with caval constriction [*97*] an inverse correlation between the output of urinary aldosterone and Na excretion was found. The most extensive observations in man on the relation of aldosterone and Na excretion in urine have been made by Bartter, Duncan and Liddle [*66,93–95*].

The relationship of the output of urinary aldosterone to Na excretion has been studied extensively by Wolff [*96*] in a large group of patients with various types and degrees of cardiac failure. In untreated patients with both right- and left-sided failure, an inverse correlation was found between renal aldosterone and Na excretion. Two-thirds of this group showed hyperaldosteronuria and Na retention whereas in the remaining third aldosterone excretion was normal and Na balance was present. The same findings were obtained in patients with pure right-sided failure. In patients with pure left-sided failure, aldosterone and Na excretion were normal. These results agree with the thesis set forth in this review and previously [*14–16,19*], that the production of aldosterone occurs in association with the continuous loss of fluid and electrolytes from the vascular bed. In patients with left ventricular failure, the relatively small volume of pulmonary vascular bed, in contrast to the remainder of the body in right-sided failure, limits the amount of fluid which can be extravasated. When this limit has been reached and fluid is no longer filtered from the blood stream, the mechanisms promoting increased aldosterone secretion cease to operate

and a new steady state is achieved. Wolff [*96*] found variable responses in aldosterone and Na excretion during therapy with either digitalis or mercurial diuretics. This finding is explicable since both therapeutic agents have a direct effect on the renal tubular transport of Na and water and digitalis therapy increases GFR. When treatment with digitalis led to improvement in myocardial function, aldosterone excretion decreased in association with a Na and water diuresis.

Muller [*98*] reported a normal rate of urinary aldosterone excretion in some patients with cardiac failure. In his study of six patients with heart failure, five were found to have a normal rate of aldosterone output, but four of them were in Na balance. The sixth patient had an increased aldosterone output and showed marked Na retention. It seems clear that if a patient is not sufficiently decompensated to retain Na, aldosterone excretion in urine may be normal.

Evidence which conflicts with the inverse relationship of aldosterone output to Na excretion was reported by Gordon in 1955 [*99*] but the data have not been published. He reported that increased aldosterone excretion in urine continued after cardiac compensation. This finding is not, however, inconsistent with observations in certain patients with primary hyperaldosteronism in whom protracted Na retention did not occur. It appears that another factor in addition to hyperaldosteronemia is needed to effect Na retention in congestive failure. In the dog with experimental heart failure it seems clear that the additional factor in question is elevated venous pressure or some consequence of it [*15,17,19,25,32,33*].

The question has been raised as to whether hyperaldosteronemia constitutes a primary mechanism which promotes the retention of Na during all stages of cardiac failure or is merely a secondary factor which contributes to Na retention late in the course of the syndrome. Available evidence supports the first alternative. During the first three weeks of experimental cardiac failure in adrenalectomized dogs [*32*] Na retention failed to occur when all hormone therapy was discontinued or during administration of hydrocortisone or cortisone alone. In dogs with cardiac failure and intact adrenals, increased aldosterone secretion in the blood of adrenal veins occurred in three dogs with failure of four, eight and thirty days' duration [*19*]. Since the GFR was frequently (four of eight dogs) normal at the onset of cardiac failure [*25,32*], the most plausible explanation for the Na retention is the high blood level of aldosterone. Hyperaldosteronuria was observed during the first eight days of experimental cardiac failure [*72*] and Na retention was almost complete during this period. Finally, it has been demonstrated that acute constriction of the inferior vena cava results in hypersecretion of aldosterone within thirty minutes [*100*].

In primary hyperaldosteronism large quantities of aldosterone are excreted in urine, yet cases in which chronic Na retention was absent have been reported [*101*]. In prolonged studies of normal dogs given large amounts of DCA [*102,103*] and in normal subjects given large doses of DCA [*104–107*] or aldosterone [*108*] no more than transient Na retention occurred. In the dog, failure of DCA to effect chronic Na retention does not appear to be related to elevated GFR [*103*] since an increased GFR was not a consistent finding during administration of 25 mg./day of DCA. August, Nelson and Thorn [*108*] reported on patients in whom endogeneous creatinine clearance was not altered by large doses of aldosterone. Also, in patients with primary hyperaldosteronism the GFR is usually within normal limits [*109*]. As suggested previously, it seems likely that additional factors are needed to effect Na retention and that Na retention is not limited by a high GFR. In the dog the presence of the additional factor of elevated venous pressure results in almost complete retention of Na when large doses of DCA are administered to adrenalectomized animals [*17*]. The response of simple adrenalectomized dogs to the injection of large amounts of DCA [*110*] was similar to that of normal dogs. It is suggested, therefore, that the presence of factors other than hyperaldosteronemia are necessary for continued Na retention.

Certain abnormalities in renal K excretion occur in congestive heart failure. During the first few days of experimental failure secondary to controlled progressive pulmonic stenosis [*25*], K balance was negative; the cardiovascular stress was marked and the negative K balance reflected tissue destruction with an associated negative nitrogen balance. However, in dogs with continued thoracic inferior vena cava constriction and ascites [*30*], K balance was positive; fecal K excretion was markedly elevated in these animals and urinary K output was strikingly decreased. (Fig. 6.) Also, in many

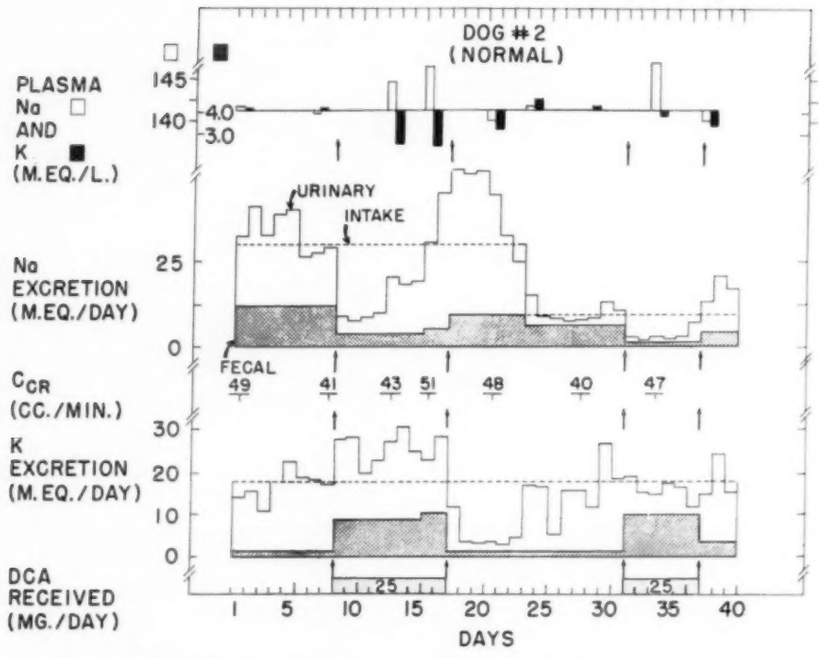


FIG. 7. Relationship of Na retention to K excretion during administration of 25 mg./day of DCA to a normal dog. A hypokalemic alkalosis developed during a Na intake of 30 mEq./day but kaluresis and hypokalemia did not occur on a Na intake of 9 mEq./day. (From: HOWELL, D. S. and DAVIS, J. O., *Am. J. Physiol.*, 179: 359, 1954 [*113*].)

patients with congestive heart failure or with hepatic cirrhosis [*48,111–112*], there was no evidence of kaluresis, hypokalemia and alkalosis. These findings are in contrast to the typical kaluresis and resultant hypokalemic alkalosis which occurs during administration of large doses of DCA to dogs [*102,103*] and man [*104–107*] and which is present in some patients with primary hyperaldosteronism [*101*]. The failure of K excretion to occur in clinical states with Na retention probably reflects the insufficiency of Na reaching the distal tubular site for exchange with K [*113*]. Evidence for this hypothesis was obtained by administration of 25 mg./day of DCA to normal dogs. (Fig. 7.) On a Na intake of 30 mEq./day, Na retention was incomplete and transient, so sufficient Na reached the distal tubule and kaluresis occurred. On a low Na intake (9 mEq./day), however, Na retention presumably was virtually complete in the proximal tubule, and kaluresis failed to occur. Also, in adrenalectomized dogs with caval constriction (Fig. 6) there was a parallelism between the decline in urinary Na and in urinary K excretion with increasing doses of DCA.

Extra-adrenal Effect of Hepatic Venous Congestion on Renal Na Excretion. As already indicated, in addition to hyperaldosteronemia, elevated venous pressure has been postulated as necessary for protracted Na retention to occur in experimental heart failure. The following experiments show the effects of a high venous pressure in the presence of constant large amounts of sodium-retaining hormone and provide evidence for the importance of the location of venous hypertension in experimental cardiac failure. In the adrenalectomized dog on a normal Na intake, 25 mg./day of DCA produced only transient retention of Na [*110,113*]. Administration of the same dose of DCA to adrenalectomized dogs with constriction of the inferior vena cava immediately above the renal veins also failed to result in sustained Na retention [*114*]. However, as shown in Figure 6, an adrenalectomized dog with constriction of the inferior vena cava above the liver had almost complete retention of Na on a dose of 25 mg./day of DCA. The principal apparent difference between the effects of a caval ligature above and below the hepatic venous outflow is that fluid and electrolytes escape readily from the vascular and lymphatic systems only with the ligature above the liver. The degree of venous hypertension below the liver and the dose of DCA were the same in both experiments. These observations indicate that, in some indirect manner, the kidney is impelled

to retain salt and water in association with the extravasation of fluid and electrolytes from the hepatic or hepatic portal bed in the presence of a normal Na intake and sufficient sodium-retaining hormone.

Also, a positive Na balance occurred in adrenalectomized dogs with thoracic caval constriction during ingestion of large quantities of Na in the complete absence of sodium-retaining hormone [*115*]. Under these circumstances fluid and electrolytes escaped from the hepatic vascular and lymphatic beds due to the high hydrostatic pressure; Na balance was positive and ascitic fluid accumulated. Presumably, the capacity of the kidney to excrete Na was exceeded, and the retained salt and water were localized in the peritoneal cavity. In contrast, the simple adrenalectomized dog did not show a positive Na balance under the same experimental conditions. These experiments indicate, therefore, that some factor associated with hepatic venous congestion influences renal Na excretion independent of aldosterone. Studies of a bilaterally adrenalectomized patient with hepatic cirrhosis and ascites [*92*] also suggested that renal Na excretion is influenced by factors other than sodium-retaining hormones; doses of cortisone which produced Na retention in this adrenalectomized patient with cirrhosis failed to cause Na retention in adrenalectomized patients without hepatic disease.

Mechanisms Leading to Increased Aldosterone Secretion. Many factors are now known to invoke stimuli which alter the rate of aldosterone secretion in normal animals [*88*]. The nature of the stimuli and of their receptors remains obscure. In clinical states with edema Peters [*14,16*], suggested that Na retention occurs in association with the extravasation of fluid and electrolytes from the blood stream when there is a resultant decrease in "effective circulating blood volume." He also proposed that adrenocortical stimulation with increased secretion of sodium-retaining hormone might occur secondary to this "leak" in the circulation and promote Na retention. Factors which alter the Starling equilibrium and promote loss of water and electrolytes from the vascular bed appear to stimulate the production of aldosterone [*116*]. This concept explains the hypersecretion of aldosterone in clinical states which otherwise differ widely, such as congestive heart failure, decompensated hepatic cirrhosis and nephrosis. In the patient with congestive heart failure a high hydrostatic capillary pressure secondary to

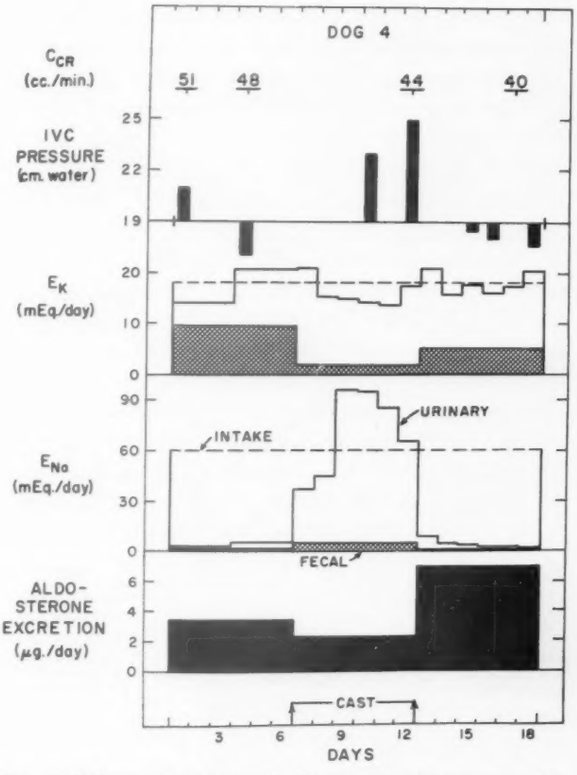


FIG. 8. Effects of a plaster body cast on aldosterone, Na and K excretion, glomerular filtration rate (C_{CR}) and inferior vena caval (ivc) pressure in a dog with thoracic caval constriction. The rate of urinary aldosterone excretion in normal dogs is less than 0.9 μg./day. (From: DAVIS, J. O. and BALL, W. C., JR., *Am. J. Physiol.*, 192: 538, 1958 [*116*].)

venous hypertension is the primary mechanism resulting in filtration of fluid from the vascular bed.

To test the hypothesis that some change occurs as a consequence of this fluid and electrolyte loss, and that the adrenal cortex is thereby stimulated, an experiment was designed to inhibit or prevent the extravasation of fluid and electrolytes. A plaster body cast was applied to dogs with caval constriction, hyperaldosteronism, Na retention and ascites [*116*]. The results of such an experiment are presented in Figure 8. During the control period aldosterone excretion in urine was increased and Na retention was almost complete. The low fecal Na and high fecal K excretion characteristic of dogs with chronic ascites (Fig. 6) was present. Application of a plaster body cast resulted in a decrease in urinary aldosterone, a reversal of the pattern of fecal electrolyte excretion toward normal, and natriuresis; the GFR declined. During recovery, the various functions returned toward or to the

control levels, with the exception of the GFR. It was suggested that aldosterone secretion was decreased as a result of an increase in intra-abdominal pressure which inhibited filtration of fluid into the peritoneal cavity.

What are the changes associated with loss of fluid and electrolytes which lead eventually to adrenocortical stimulation? Initially, there is a decrease in total circulating blood volume which occurs in association with hypersecretion of aldosterone [*100*]. This decline in total vascular volume is not essential, however, because infusion of dextran to maintain or to increase blood volume during bleeding [*117*] and during acute caval constriction [*100*] failed to prevent the increase in aldosterone secretion. Also, in congestive failure [*118,119*] and decompensated cirrhosis of the liver [*120*] the circulating blood volume frequently is elevated. These data do not exclude the possible effect of a local decrease in vascular volume but there is as yet no evidence that such a local decrease occurs in congestive failure.

Gann, Bartter and Mills [*121*] have suggested that the stimulus to increased aldosterone secretion is decreased pulse pressure. Pulse pressure decreased in association with hypersecretion of aldosterone in their anesthetized dogs following both caval constriction and common carotid artery constriction. In more prolonged observations, however, the pulse pressure was normal in four of six dogs with thoracic caval constriction and ascites [*30*]. Attempts to produce chronic left ventricular failure in the dog by induction of marked aortic stenosis and reduced pulse pressure have not resulted in Na retention [*114*]. Also, it should be pointed out that patients with aortic stenosis and a narrowed pulse pressure may live for years without edema.

Pearce [*122*] and Atkins and Pearce [*123*] have evaluated the possible role of cardiac atrial and carotid sinus receptors in mediation of the effect of plasma volume expansion by either plasma or iso-oncotic albumin solutions. Natriuresis was not prevented, but was diminished by bilateral cervical vagotomy. Carotid sinus denervation alone or combined with vagotomy also failed to prevent the diuresis in most experiments; in a few instances the response was absent or diminished. Diuresis and natriuresis occurred during infusion into adrenalectomized animals. This result indicates involvement of a non-adrenocortical mechanism but does not exclude a decline in aldosterone secretion. Although GFR usually increased, the changes were neither large nor consistent in direction, a finding which the authors interpreted as indicating that factors other than increased GFR were involved.

At the Laurentian Hormone Conference (1958), Bartter et al. [*124*] suggested that receptors in the carotid sinus are concerned with the regulation of aldosterone secretion. They reported that constriction of the common carotid arteries proximal to the carotid sinus increased the output of aldosterone in the adrenal veins of anesthetized dogs and that the increase was prevented by previous section of the carotid sinus nerve; also, that hypersecretion of aldosterone, the usual response to acute thoracic caval constriction, did not occur if the carotid sinus nerves had been sectioned previously.

To examine the possible role of carotid sinus and aortic arch receptors in the pathogenesis of hyperaldosteronism following thoracic caval constriction, the effects of carotid sinus denervation on aldosterone and Na excretion were studied in trained unanesthetized dogs [*125*]. Following carotid sinus denervation of normal animals, aldosterone output in the urine remained normal; Na balance was maintained and there was no evidence of hypokalemia. These animals were then subjected to constriction of the thoracic inferior vena cava; the usual response of hyperaldosteronuria, marked Na retention and ascites occurred. Subsequent bilateral cervical vagotomy was without effect on hyperaldosteronuria in two of three dogs; a slight increase in Na excretion occurred but a positive Na balance and ascites formation continued. Because of these negative results in long-term experiments, the effects of both acute and chronic carotid sinus denervation on the aldosterone output by the adrenal were studied in anesthetized dogs. The rates of aldosterone secretion were normal after either acute or chronic carotid sinus denervation. Also, aortic depressor nerve section was without effect on aldosterone and Na excretion in rabbits. These findings thus offer no support for the concept that a volume receptor is located in the carotid sinus or aortic arch.

More recently, Bartter, Mills and Gann [*126*] reported that denervation of the thyroid-carotid arterial junction rather than the carotid sinus prevented hypersecretion of aldosterone following thoracic caval constriction or bilateral common carotid artery constriction. This de-

nervation procedure involves interruption of the nerve supply to the common carotid and thyroid arteries in the region of the origin of the latter. These observations of Bartter and associates are at variance with a more recent attempt [*114*] to locate a nerve receptor in the central arterial system. Denervation of the entire cervical carotid arterial system including the carotid sinus and thyroid-carotid arterial junction failed to influence the high rate of aldosterone secretion, Na retention and the formation of ascitic fluid in dogs with thoracic caval constriction.

Another region which has been considered as a location for receptors regulating aldosterone secretion is the right atrium. Farrell [*88*] has suggested that hypersecretion of aldosterone following thoracic caval constriction results from a reflex mediated by right atrial stretch receptors. Anderson, McCally and Farrell [*127*] found that stretching the right atrial wall with external sutures was associated with an abnormally low rate of aldosterone secretion but left atrial stretching was without effect. Also, Anderson, McCally and Farrell [*128*] have reported that cooling the vagus nerve to 0°c. was associated with hyposecretion of aldosterone.

Several lines of evidence may be cited against the hypothesis of Farrell and associates. First, this hypothesis leaves unexplained the marked increase in aldosterone secretion in experimental cardiac failure [*19*], in which the right atrial pressure is always high. Secondly, the finding that right atrial stretching results in hyposecretion of aldosterone does not necessarily indicate that a reflex operates in the opposite direction, namely, that an increase in aldosterone secretion occurs in the presence of a low pressure or volume in the right atrium. Thirdly, if receptors for the regulation of aldosterone secretion are located in the right atrium, cervical vagal section should prevent the increase in aldosterone secretion following acute thoracic caval constriction, and aldosterone production should decline following bilateral cervical vagotomy in dogs with chronic caval constriction and secondary hyperaldosteronism; neither occurs. Mills, Casper and Bartter [*129*] found that dogs with both vagi cut in the neck showed essentially the same increase in aldosterone production following caval constriction as normal dogs with intact vagi. In a dog with chronic caval constriction and a high rate of aldosterone output, acute bilateral cervical vagotomy was without effect on aldosterone secretion [*114*]. Also, in protracted studies of aldosterone and Na excretion in dogs with chronic thoracic caval constriction, hyperaldosteronism, Na retention and ascites continued after bilateral cervical vagotomy [*125*]. There is, therefore, little support for the hypothesis that right atrial stretch receptors control aldosterone secretion in experimental secondary hyperaldosteronism in the dog.

The role of the anterior pituitary in the control of aldosterone secretion has been studied extensively [*43,44,95,97,130–142*] but only recently [*132,136–139*] has the importance of anterior pituitary function become clearly evident. In early reports [*43,44,95,97,130–131*], most investigators delegated a secondary supportive function to the anterior pituitary hormones. Farrell, Rauschkolb and Royce [*43*] reported only a moderate reduction in aldosterone secretion after hypophysectomy. Hyperaldosteronuria, marked sodium retention and ascites occurred in the absence of the adenohypophysis in dogs with thoracic inferior vena cava constriction [*97*]. Also, urinary aldosterone excretion was within normal limits in some patients with hypopituitarism [*131*].

The important influence of the anterior pituitary on aldosterone production was first indicated from results obtained after acute hypophysectomy. In rats, Singer and Stack-Dunne [*133*] reported an 83 per cent reduction in aldosterone secretion following hypophysectomy. Ganong and associates [*134*] also found aldosterone output of the adrenal veins 83 per cent lower after hypophysectomy. In experimental secondary hyperaldosteronism [*132*], a 76 to 97 per cent decrease in aldosterone secretion occurred within one to two hours following removal of the anterior pituitary and the magnitude of the change was not sufficiently different from the observed fall in corticosterone output. Administration of ACTH immediately following hypophysectomy of dogs with secondary hyperaldosteronism completely blocked the usual marked decrease in aldosterone and corticosterone secretion.

In patients with hypopituitarism or in hypophysectomized patients, most of the observations have been limited to studies on urinary aldosterone excretion. Because of the wide range of normal values it has been difficult to evaluate aldosterone secretion from measurements of urinary aldosterone output. Nevertheless, Hernando et al. [*135*] and, more recently, Ross and

associates [*136*] have reported values below or at the lower limit of normal for urinary aldosterone excretion in several patients with decreased or absent anterior pituitary function. Also, the response to Na restriction [*135,136*] and to surgical stress [*136*] was frequently reduced in these patients.

The importance of ACTH in the control of aldosterone secretion has been demonstrated by several types of evidence. First, it has been reported repeatedly [*43,95,132,135–138*] that administration of exogeneous ACTH increased aldosterone secretion and urinary aldosterone excretion. Secondly, large doses of cortisone given to inhibit ACTH production caused a striking fall in both aldosterone and corticosterone secretion in dogs with thoracic caval constriction [*137*]. Thirdly, studies of aldosterone secretion in conscious dogs [*139*] have demonstrated a striking difference in the basal rate of aldosterone secretion and the output following "stress." Finally, bleeding effected a three-to-fourfold increase in Porter-Silber chromogens and corticosterone secretion as well as in aldosterone output [*140,141*].

Further evidence for the importance of the anterior pituitary and, specifically, of ACTH has been obtained by attempts to stimulate aldosterone secretion in hypophysectomized dogs [*137–141*]. A low sodium diet [*137*], acute constriction of the thoracic inferior vena cava [*137*] and bleeding [*140–142*] have all failed to result in hypersecretion of aldosterone. Bleeding appeared to be the most effective of the three types of stimuli and resulted in an increase from a very low posthypophysectomy level to the average normal value [*142*].

The only reported situation in which actual measurements of aldosterone secretion show hypersecretion in the absence of the anterior pituitary was following hypophysectomy of conscious dogs with thoracic caval constriction [*139*]. In these animals, anterior pituitary ablation resulted in a marked reduction in aldosterone secretion but in some dogs aldosterone secretion remained elevated six times the normal or control level. Also, in conscious dogs with thoracic caval constriction but otherwise intact, very high (presumably maximal) rates of aldosterone secretion occurred in the presence of very low basal outputs of corticosterone and Porter-Silber chromogens [*139*]. Available data show, therefore, that in secondary hyperaldosteronism the plasma level of ACTH need not necessarily be elevated, but a normal plasma level appears essential for the very high rate of aldosterone secretion observed in intact animals. It is concluded that ACTH supports the biogenesis of aldosterone at a high level in secondary hyperaldosteronism.

Studies of the role of the neurohypophysis in experimental secondary hyperaldosteronism indicate that antidiuretic hormone is not essential for sustained Na retention and ascites formation. Hamilton and associates [*143*] damaged the neurohypophysis and produced diabetes insipidus in dogs with caval constriction and ascites; Na retention and ascites formation continued unabated. Laragh and co-workers [*144*] produced diabetes insipidus by destruction of the neurohypophysis and subsequently constricted the thoracic inferior vena cava. Sodium retention and ascites formation occurred, and the only observed effect of the neurohypophysial lesion was the continued increase in water turnover.

The possibility of peripheral nerve receptors and an afferent neural limb raises the question of a central integrating mechanism in the control of aldosterone secretion. Indeed, there are several reports of attempts to localize centers in the central nervous system for the regulation of aldosterone secretion. In 1956 Rauschkolb and Farrell [*145*] suggested that the diencephalon contains a center for control of aldosterone secretion. They found that decerebration and removal of brain tissue anterior to the mid-brain was followed by a marked reduction in aldosterone output, whereas decortication was without effect. No mention was made of the fate of the anterior pituitary. If the adenohypophysis was removed or severely damaged by decerebration and mid-brain section, this alone might account for the low rate of aldosterone secretion after decerebration in view of the striking fall in aldosterone production following hypophysectomy [*43,132*].

More recently, additional attempts have been made to locate a hypothalamic center for the regulation of aldosterone secretion. Newman, Redgate and Farrell [*146*] reported a rapid increase in aldosterone secretion following creation of ventral hypothalamic lesions in cats, but damage to the anterior pituitary or its blood supply could not be excluded. Daily and Ganong [*147*] found that ventral hypothalamic lesions were without effect on electrolyte excretion during a low Na intake and during K loading. Ganong

and co-workers [*134*] also have studied the effects of chronic hypothalamic lesions on aldosterone secretion. They reported that the only hypothalamic lesions which influenced aldosterone production were those including the median eminence. In their dogs with chronic median eminence lesions the acute response in aldosterone secretion to the surgical stress of adrenal vein cannulation was reduced. These findings are supported by studies of the effects of hypothalamic lesions in dogs with experimental ascites [*148*]; decreased urinary aldosterone output occurred only in dogs with hypothalamic lesions which included the median eminence. Available data indicate, therefore, that lesions of the median eminence influence aldosterone secretion; the effect may be mediated through ACTH release. Evidence is lacking to support the concept that hypothalamic areas other than the median eminence regulate aldosterone production.

Newman and associates [*146*] have also presented evidence derived from brain stem lesions that the central nervous system is involved in the regulation of aldosterone secretion. They reported that cats with lesions in the central core of the mid-brain and caudal diencephalon secreted aldosterone at a lower rate than normal animals whereas cats with lesions in the rostral pons had a higher rate of aldosterone output than normal animals. If a central integrating mechanism is involved in the control of aldosterone secretion, it might be expected that lesions in the brain stem would influence aldosterone secretion. However, conclusive evidence for the importance of the central nervous system in the control of aldosterone secretion awaits additional studies. The finding [*142*] that the response in aldosterone secretion to bleeding in decapitated dogs (increased from .007 to .022 μg./min.) was essentially the same as in hypophysectomized dogs, raises the question as to the importance of a central integrating mechanism.

That neural connections to the adrenal gland are unnecessary for aldosterone secretion and maintenance of normal electrolyte metabolism in dogs was suggested by Levy and Blalock in 1939 [*149*]. They transplanted one adrenal gland to the neck and removed the other adrenal. These animals appeared to be normal for several months, and one animal withstood the stress of pregnancy and gave birth to a normal puppy. More recently, Fleming and Farrell [*150*] transplanted one adrenal to the thigh in dogs and found a normal or elevated rate of aldosterone output. Also, in studies of unanesthetized sheep, McDonald, Goding and Wright [*151*] transplanted one adrenal to the neck and removed the remaining adrenal gland; normal plasma electrolyte concentrations and a normal response in salivary electrolyte excretion to Na depletion were observed.

Suggestive evidence of a hormonal mechanism other than ACTH has been reported [*74,152,153, 155–157*]. Studies [*152*] of rats on a low Na diet showed that the animals excreted a substance in urine which increased the excretion of aldosterone in feces. Also, Mulrow and associates [*153*] have reported that a factor in human urine promotes aldosterone production *in vitro* in the adrenal glands of the rat. More direct evidence for a hormonal mechanism was obtained by measurement of aldosterone secretion in adrenal vein plasma from isolated adrenals of normal dogs during cross circulation of blood from dogs with chronic thoracic caval constriction and secondary hyperaldosteronism [*74*]. The technic of adrenal isolation employed was that of Hilton et al. [*154*]. The control and recovery rates of aldosterone secretion were determined with the normal recipient's blood. During cross circulation, a 134 per cent (average for nine dogs) increase in aldosterone secretion occurred in the adrenal vein plasma from the isolated adrenals of the normal recipient. Observations during cross circulation of blood from normal dogs into the isolated adrenals of normal animals showed that aldosterone secretion was usually unchanged or decreased. Since no consistent alterations in electrolyte concentration occurred, the data indicate that a humoral agent from dogs with experimental ascites stimulated hypersecretion of aldosterone in the normal isolated adrenals. It was suggested that this aldosterone stimulating hormone constitutes the humoral mechanism in experimental secondary hyperaldosteronism in the dog.

Concurrent independent evidence for this hormone was obtained in unanesthetized sheep by a group of Australian workers [*155*]. They found that cross circulation of blood from an adrenalectomized animal on a low Na intake through an adrenal gland transplanted to the neck of a normal recipient sheep resulted in a marked decrease in the salivary Na:K ratio.

Farrell and associates [*156,157*] have suggested

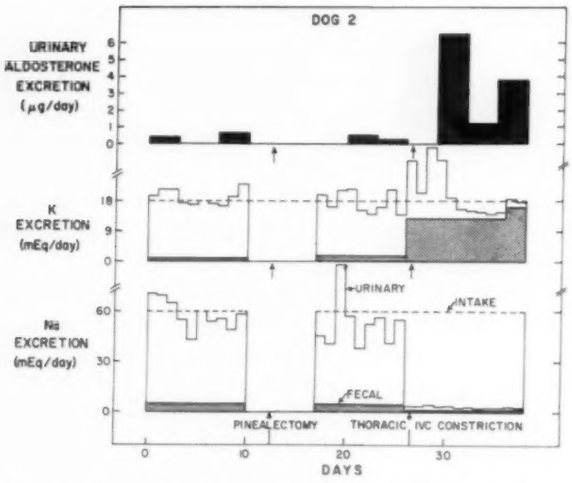


FIG. 9. Effects of pinealectomy and subsequent constriction of the thoracic inferior vena cava on aldosterone, Na and K excretion. The typical response to caval constriction occurred. The pineal gland was identified in the material removed at surgery and sections of the pineal region showed no evidence of the pineal gland. The posterior commissure, habenular commissure and subcommissural body were destroyed.

that the aldosterone-stimulating hormone is secreted by the pineal gland. Removal of the pineal gland or some associated structure was reported to result in decreased aldosterone secretion [*156*] and extracts of pineal tissue selectively increased aldosterone output in the decerebrate dog [*157*]. No evidence, however, was offered for the identity of the stimulating substance or effect with that of the hormone circulating in peripheral plasma [*74*]. An attempt [*114*] to confirm Farrell's effect of pineal ablation has yielded a negative result. Three normal dogs were subjected to pinealectomy and subsequent constriction of the thoracic inferior vena cava. (Fig. 9.) No effect of pinealectomy on Na, K and aldosterone excretion was observed. Following caval constriction the typical syndrome of experimental secondary hyperaldosteronism resulted and measurements of aldosterone output of the adrenal veins showed hypersecretion. Serial sections of brain in the pineal region showed no evidence of the pineal gland; in two of the dogs the posterior commissure, habenular commissure and subcommissural body were destroyed.

Summary of the Public Sequential Changes Between the Primary Myocardial Defect and the Kidney in Congestive Heart Failure. Studies of patients with cardiac decompensation have demonstrated that the cardiac output may be either elevated or low in the presence of Na retention [*158,159*]. The same relationship has been observed in dogs with experimental heart failure [*25,51*]. These observations suggest that the sequence of events leading to Na retention is not initiated by an alteration in the absolute level of the cardiac output. The factor common to dogs with low and high output failure and to dogs with thoracic caval constriction is elevated venous pressure. In these experimental situations Na retention and ascites formation were observed only in the presence of an elevated venous pressure of at least 7 cm. of water above the normal control level.

A high hydrostatic pressure favors the movement of fluid and electrolytes from the vascular bed into the tissue spaces. The loss of fluid and electrolytes results in an immediate decrease in circulating blood volume but the decreased volume is rapidly replenished by retention of salt and water. The compensatory mechanisms may overshoot, establishing a state of increased blood volume in patients with congestive heart failure [*118,119*] and decompensated hepatic cirrhosis [*120*]. The blood volume is increased also in experimental heart failure [*25*].

It is not clear that the initial loss of vascular fluid occurs before the adrenal cortex is stimulated to secrete aldosterone but certain observations support this view. Ball and co-workers [*33*] demonstrated the formation of an initial pool of ascites in the absence of a positive Na balance in dogs with overt signs of congestive heart failure. This was accomplished by withholding dietary Na during the first few days after production of severe pulmonic stenosis. Irrespective of the precise sequence of events, the adrenal cortex has been stimulated to secrete aldosterone within thirty minutes following the production of a high venous pressure and resultant extravasation of fluid and electrolytes [*100*].

If a decrease in vascular volume rather than some other change secondary to fluid and electrolyte loss provides the stimulus to aldosterone production in heart failure, the decreased volume must be local in the region of a receptor; measurements of total vascular volume show unequivocally that aldosterone secretion may be markedly increased in association with increased total vascular volume. Evidence for such a local decrease in vascular volume in congestive failure is lacking. Following acute caval constriction the pressure and probably the

volume of blood in the right atrium falls [*114*]. This acute decrease in right atrial pressure is transitory, as is the decrease in total blood volume and pulse pressure. In dogs with continued caval constriction, a right atrial pressure lower than the normal control level was not demonstrable ([*125*] and personal observations). The lowest common denominator for all available data on congestive failure is that some functional change secondary to fluid and electrolyte loss stimulates aldosterone production.

It is still uncertain whether or not a central integrating mechanism is involved in the control of aldosterone secretion. The striking drop in aldosterone output of the adrenal veins following hypophysectomy of dogs with experimental secondary hyperaldosteronism emphasizes the important role of the anterior pituitary in aldosterone production. The anterior pituitary hormones support steroidogenesis of aldosterone by the adrenal cortex at a very high level. The immediate stimulus to aldosterone production appears to be a hormone which we have tentatively designated, the aldosterone stimulating hormone. The origin and chemical nature of this hormone remain unknown.

A decrease in the rate of inactivation of aldosterone by the liver may contribute to the high blood level of aldosterone.

The increase in circulating aldosterone constitutes one of the important primary mechanisms leading to Na retention in heart failure. Changes in glomerular filtration rate also play an important role in the regulation of sodium excretion by the kidney in congestive failure.

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Traumatic Asphyxia*

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TRAUMATIC asphyxia, also known as *Masque Ecchymotique* and by many other synonyms,§ is a distinct and unforgettable syndrome characterized by bluish red to bluish black discoloration of the skin of the face and neck, and usually of the shoulders and upper chest, with massive subconjunctival hemorrhage. In most instances it results from severe compression or injuries that squeeze the thorax and/or upper part of the abdomen with complete or partial cessation of respiration for varying periods of time.

This condition was first noted in 1837 by Ollivier [*1*] who observed persons crushed to death in mob violence. However, it was not until 1900 that Perthes [*2*] gave the first complete description of the clinical picture. In 1946 Dwek [*8*] collected and summarized 170 cases from the literature. Since that time nine additional cases (including the present one) have been recorded [*10–17*].

This disorder is mentioned in only one [*18*] of six current textbooks of Internal Medicine [*18–23*] and has received little attention in American periodicals designed for the internist. The purpose of this paper is to report on a patient with traumatic asphyxia and to review the subject of traumatic asphyxia.

CASE REPORT

On the afternoon of September 4, 1958, a nineteen year old white male student mechanic was lying on the ground directly beneath and approximately parallel with the tail section of a stationary jet aircraft. The nose and tail sections of the plane were not anchored to the ground and the plane's normal parked attitude was dependent upon equal ballast both fore and aft. When fuel was withdrawn from the nose tanks the plane's center of gravity shifted, causing the aircraft to settle tail downward. Although the patient attempted to roll out of the path of the descending tail section, he was struck over the area of the left scapula and was pinned to the ground on his right side. He remained trapped for approximately fifteen seconds before he was freed. (The accident was reproduced later, and by use of reliable electrical scales it was determined that the weight sustained by the patient was 1,400 pounds.) The patient recalled that when the accident occurred he had the sudden sensation of tremendous pressure in the upper part of his body, after which he momentarily lost his vision. He felt as if his eyes were going to "pop out" and as if his head were going to "blow up." Observers at the scene noted that the eyes of the patient became quite prominent and that the neck and face first turned bright red and then dark blue. About a minute after the mishap occurred, the patient had a generalized clonic seizure which was accompanied by urinary and fecal incontinence. He was then brought to the hospital.

In the emergency room the patient was rational but extremely restless. He complained of severe pain in the upper left quadrant of the abdomen which was aggravated by breathing. Respirations were 24 per minute and were shallow, irregular and grunting in character. The blood pressure was 120/80 mm. Hg in both arms and the pulse was strong and regular at 84 per minute. Rectal temperature was 99°F. The skin was cool and moist.

The skin over the entire face and neck was dark blue and blanched on pressure. (Fig. 1.) During the first examination this discoloration appeared uniform, but closer inspection revealed the bluish background to be studded with many petechial hemorrhages. These skin changes were less marked over the ears and about the hair line. Many petechiae covered the right upper anterior part of the chest and shoulder, but no other cutaneous abnormalities were noted. Although the lips were blue, the buccal mucosa and fingernails were pink. Massive pharyngeal and sublingual ecchymoses were present. (Fig. 2.) In addition, there were striking bilateral subconjunctival hemorrhages from the superior limbus inferiorly which elevated the conjunctivas from the globes. The conjunctiva above the superior limbus was unaffected. (Fig. 3.) The upper and lower lids of both eyes showed moderate edema and ecchymosis. The optic fundi

§ Druckstauung [*2*], Stauungsblutungen nach Rumpfcompression [*3*], traumatic cyanosis [*4*], traumatic apnea [*5*], stasis cyanosis [*6*], pressure stasis [*7*], ecchymotic mask [*8*], cervicofacial cutaneous asphyxia [*9*], the symptom complex of Perthes [*9*].

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FIG. 1. Day 1. The striking bluish black discoloration of the face and neck is shown.

showed mild venous congestion without papilledema or hemorrhages. There was no bleeding or drainage from the ears or nose. No cervical venous distension was noted. There was marked splinting of the entire thorax and there were decreased breath sounds in the left lower lobe of the lung. Initial examination of the heart was non-contributory. Marked tenderness was present in the left upper quadrant of the abdomen and over the region of the left kidney. Neurological examination was within normal limits.

Laboratory data were as follows: on the day of admission the total white blood cell count was 30,800 per cu. mm. with a differential of 90 per cent neutrophils, 9 per cent lymphocytes and 1 per cent monocytes. The volume of packed red cells was 40 per cent and the results of urinalysis were normal. The venous pressure in both arms equaled 9 cm. of normal saline. The serum transaminase measured 54 units and the blood urea nitrogen was 11 mg. per cent. Thereafter, many urinalyses, as well as frequent determinations of the total and differential white blood cell count, volume of packed red cells and blood urea nitrogen were all within normal limits. The venous pressure was repeated on the third hospital day and was found to be unchanged. The serum transaminase rose to a high of 78 units on the fourth day, after which it remained normal.

A spinal puncture between the fourth and fifth lumbar vertebrae performed a week after admission revealed an initial pressure of 180 mm. of water, clear cerebrospinal fluid, 5 lymphocytes per cu. mm. and a protein of 15 mg. per cent.



FIG. 2. Day 6. Note the massive subconjunctival hemorrhage, the sublingual hemorrhage and the petechiae over the right shoulder. Marked clearing of the facial discoloration has occurred.

Serial electrocardiograms were normal, except on the second hospital day when inverted T waves and flattened P waves were noted in leads II, III and aVF.

The only abnormalities seen in multiple roentgenograms of the chest were simple fractures of the fourth, fifth, sixth, seventh, and eighth left posterior ribs, together with a change in the cardiac contour to be described in the hospital course. Roentgenograms of the skull, the entire vertebral column, pelvis and both shoulders demonstrated no alteration in the bony structures. Fluoroscopic examination of the heart and lungs and an intravenous pyelogram obtained during the second week of hospitalization essentially showed no abnormalities.

The hospital course was as follows: approximately ten minutes after admission an extraordinary sound developed over the precordium. It was heard best along the left sternal border at the fourth interspace, in



FIG. 3. Day 9. The unaffected portions of the conjunctivas are demonstrated. The skin of the face is now normal except for bilateral periorbital ecchymoses.

the supine position, and was not altered by respiration. One could palpate a shock in this area but no true thrill or murmur was detected. This peculiar sound was extremely loud and painful to the examiner's ear. It appeared during systole and resembled closely the "pop" of a steam radiator. It was followed occasionally by two other short systolic noises, and when all three sounds were present they resembled "a snap, crackle and pop" sound. There was no associated chest pain or subcutaneous emphysema. A portable roentgenogram of the chest and electrocardiogram performed at this time were not considered abnormal. No phonocardiograph was available. The etiology of the new physical finding remained obscure, although the pericardium was thought to be the site of its origin.

About twenty minutes after these new sounds developed the pulse suddenly became weak, the intensity of the heart tones diminished, the neck veins became slightly distended and the patient complained of increasing shortness of breath. Cardiac tamponade was suspected and while standard lead II of the electrocardiogram was being recorded, a pericardiocentesis was performed in the fourth interspace at the mid-clavicular line. Sixty cubic centimeters of bright red fluid was removed and the patient's condition immediately improved. Another portable roentgenogram of the chest demonstrated a 1.5 cm. decrease in the transverse diameter of the heart. Shortly thereafter, left lower quadrant paracentesis of the abdomen produced no evidence of intraperitoneal bleeding.

In the subsequent hours the patient received fluids intravenously, oxygen via nasal catheter and narcotics. The administration of the oxygen had no effect on the discoloration of the skin or lips. During one examination on the second hospital day an apical pericardial friction rub was heard. Approximately seventy-two hours after admission the previously described unusual precordial noises abruptly disappeared. Thereafter the patient was asymptomatic, and all medications were discontinued. On the fourth hospital day a transient pleural friction rub developed over the lingula. The marked bluish discoloration of the face and neck gradually cleared by the end of the first week and only the periorbital tissues exhibited the usual chromatic changes seen in healing ecchymoses. The sublingual and pharyngeal hemorrhages, together with the petechiae over the right upper anterior part of the chest and shoulder, resolved completely within ten days. The subconjunctival hemorrhages remained unchanged for the first seven days, after which they gradually faded and were replaced by a dark yellow hue. A month passed before the eyes regained a normal appearance.

The temperature reached a high of 101°F. between the second and fifth day, but it was normal thereafter. The blood pressure remained stable and at no time did chest pain, cough or hemoptysis develop.

The patient was gradually ambulated at the end of the first week and was discharged to duty sixty-seven days after admission.

COMMENTS

Clinical Summary. The striking discoloration of the head, neck and upper part of the thorax and the brilliant red conjunctivas are the characteristic lesions from which traumatic asphyxia derives its name.

Skin. The skin presents a marked bluish red to bluish black discoloration which usually fades or disappears upon pressure [*24,25*]. It appears to be uniform at first glance, but on closer examination one may see petechiae, small ecchymoses and irregular patches of normal skin scattered throughout the affected areas. One patient showed petechiae alone [*26*].

The discoloration typically covers the face and neck. It may be more pronounced about the eyelids, nose and lips and less marked or absent about the ears [*27,28*]. It may or may not involve the scalp. Usually it is more irregular and less intense below the face and neck, where it most frequently involves the upper thorax; it may extend to the level of the nipples anteriorly and to the lower border of the scapulas posteriorly, producing the so-called "double trapezius triangles" [*24,29,30*]. Less commonly the discoloration spreads to the upper arm as far as the insertion of the deltoid muscle [*25,31*] to the axillary regions [*25,32*] and rarely to the bend of the elbow [*8*]. In one patient a small transverse strip of discolored skin about three inches wide appeared just above the umbilicus [*25*]. This might have been due to an abnormally free anastomosis of the thoracoabdominal blood vessels.

The discoloration is often symmetrical, but one side may be more involved than the other [*33–35*]. Furthermore, under points of pressure, such as the collar band or hat band, the skin may be perfectly normal [*36*]. In such cases there is a striking line of demarcation between the normal and abnormal areas.

Maximum discoloration may not appear until several days after the accident [*9,29,31–33,37*]. However, it usually begins to clear on the second to fourth day and disappears within two weeks. In most cases it does not undergo any chromatic changes while healing [*4,25,27,38*], and the administration of oxygen does not alter the discoloration significantly [*38,39*].

Frequently, there is a marked swelling of the tissues of the neck and face, especially the eyelids

and lips [*8,36,40–43*]. This may be so intense that the patient's age and ordinary appearance cannot be guessed [*28,29*]. Multiple abrasions and lacerations of the skin are common.

Eyes. The lids show the characteristic cutaneous discoloration with or without extravasated blood. They are often swollen, sometimes to the extent that the patient cannot open his eyes [*8*].

Bright red subconjunctival hemorrhage is a characteristic of traumatic asphyxia and forms a striking contrast to the blue skin of the face. Only very rarely is it absent [*44*]. It is typically extensive, bilateral and symmetrical, although one eye may be more involved than the other [*34,45*]. It commonly covers the interpalpebral areas only, but as in our patient, that portion below the inferior limbus may also be affected. Rarely, the entire bulbar conjunctiva may be involved [*43*]. The hemorrhage remains unchanged for about a week, after which it slowly fades and is replaced by a yellow hue. Within a month, in most instances, the conjunctivas regain a normal appearance. However, in one case, cyanosis of the conjunctivas was still present one year after the accident [*8*].

There may be marked edema of the bulbar and palpebral conjunctivas. This may cause the eyes to appear proptotic and the patient may have difficulty in closing the lids.

The margins of the cornea may show a bluish tinge [*17*].

Exophthalmos occurs in about one-fifth of the patients [*36*] and is sometimes unilateral [*46*]. It is probably due to a combination of hemorrhage, edema and congestion in the orbit [*17*] and usually regresses along with the other ocular manifestations [*8*].

The pupils may show transient miosis or mydriasis and may not react to light [*36*]. Such changes may be unilateral or bilateral and may or may not be accompanied by visual disturbances.

Ocular palsies are distinctly rare, having been reported in only three cases [*36,47*]. They may produce temporary diplopia [*47*] or complete paralysis of the globes [*36*].

The ophthalmoscopic examination has been non-contributory in many patients, while in others it has revealed a wide variety of monocular [*46,48*] and binocular abnormalities. These have included papilledema [*17*], hemorrhage into the vitreous [*48*], and changes in the retina such as hemorrhages [*36*], exudates [*49*], hyperemia [*36*], congestion [*46*] and edema [*38*]. Berrisford [*50*] observed blurring of the discs and discrete bluish grey elevated patches in the peripheral portions of the fundi in his patient; the lesions resembled opaque nerve fibers and disappeared within several days. Thrombosis of the central retinal artery occurred in one patient [*36*]. Optic atrophy has been a late complication in a few persons [*36,45,46,49*], some of whom showed no previously visible ophthalmoscopic changes [*17*].

Perimetric examination has not been utilized frequently. However, paracentral scotomas [*38*], central scotomas, and varying degrees of contraction of the visual fields have been found [*36*].

The vision remains normal in many patients, whereas in others it may be impaired or lost immediately in one [*46*] or both eyes [*2,7–9,48*]. Occasionally, such impairment has not developed until several days [*51*], weeks [*43*], or even months [*45*] after the accident. The disturbances often clear completely within twenty-four hours [*7,9*], but may persist for three months [*36*]. Not infrequently the damage is permanent. These visual defects have occurred in the absence of retinal hemorrhage and have been attributed, therefore, to indirect trauma to the optic nerve with secondary optic atrophy or to retinal degeneration secondary to vascular stasis and edema [*36*].

Mouth. The discoloration noted in the skin may also involve the mucous membranes of the mouth, but more commonly one sees petechiae or ecchymoses in the pharynx [*52,53*], hard and soft palate [*31,38*], on the buccal surfaces [*38,40,47,53*], or under the tongue [*31,38,54,55*]. The tongue may be so swollen [*38,56*] that speaking and swallowing become difficult [*25*].

Nose. Other than the typical cutaneous discoloration, epistaxis is the only abnormality commonly affecting this organ [*5,8,11,31,43,44,57*].

Ears. There may be petechiae or ecchymoses within the tympanic membranes and external auditory canals [*25*]. Otorrhagia may exist with or without rupture of the ear drum [*5,11,41,43, 57,58*]. In some cases transient tinnitus [*44*] or deafness [*9*] occur, and very rarely cerebrospinal fluid may drip from the ears [*59*].

Respiratory Tract. Pulmonary abnormalities are common and have consisted of cough [*35*], hemoptysis [*24,36,54*], pulmonary edema [*9*], hemothorax [[*36*], pneumonia [*35*], multiple abscesses [*58*], empyema [*58*], pleural effusion [*47*], subcutaneous emphysema [*30,43*], and rarely open thoracic wounds [*30,43*]. Severe

chest pain and dyspnea [*13,24*] are common early in the hospital course, even when the roentgenograms of the chest reveal no abnormalities [*8*]. Occasionally, cough, hemoptysis and fever develop on or about the third day and last for several days. This has been referred to as "contusion pneumonia" [*25,29,35*].

Two patients have shown marked difficulty in talking above a whisper. This lasted as long as several months and was thought to be due to hemorrhage into the vocal cords [*43*].

Heart. Cardiac abnormalities have been recognized rarely in traumatic asphyxia. In Ettinger's patient reported on by Laird and Borman [*35*] dilatation of the heart was noted, and Shimonek [*56*] reported a patient in whom "the heart was beating against the chest wall with great vigor." In another patient reported on by Laird and Borman [*35*] "the cardiac action was unduly prominent, the precordium heaving. The cardiac apex was visible and palpable in the fourth interspace 6 cm. to the left of the midsternal line. There was a loud slapping systolic murmur, heard best over the apex. A crackling sound was heard over the fourth interspace to the left of the sternum. The second heart sound over the lower sternum was pistol-shot, clear, and ringing in quality. During the height of inspiration, breath being held, the crackling sounds practically disappeared. When the breath was held at the end of expiration, the sounds were intensified. The labored cardiac action subsided at the end of the first week and the crackling sounds heard over the sternum disappeared at the end of the second week." These investigators did not attempt to explain the pathogenesis of the precordial noises in their patient, and we have no satisfactory explanation for the somewhat similar auscultatory phenomena observed in our patient. The pericardial effusion in our patient is thought to have resulted from a laceration of the parietal pericardium, and it is of interest that this complication has not been described in any other patient with traumatic asphyxia. It may be, however, that cardiac lesions have been overlooked in previous cases, since injury to the myocardium or pericardium following non-penetrating chest trauma is often well tolerated and does not always produce significant clinical findings [*60*]. Therefore, it would seem wise to consider the possibility of cardiac injury in every victim of traumatic asphyxia.

Gastrointestinal. Abdominal pain is frequent, but distention [*24*], vomiting and rigidity are uncommon [*8*]. Dysphagia may occur without apparent cause [*16*] or in association with a pharyngeal hematoma [*33*] or swollen tongue [*25*]. Perforating wounds of the abdomen with hemoperitoneum are encountered rarely [*43*]. A patient with hematemesis [*40*] and another with bleeding from the rectal mucosa [*61*] have been described.

Genitourinary. Temporary urinary retention is not uncommon [*62*]. Heuer [*36*] described a patient who had a fracture of the pubis and ischium which produced a tear in the urinary bladder; Henry [*58*] reported on a patient who suffered a puncture wound of the perineum.

Nervous System. About one-third of the patients are unconscious [*31*]. The unconsciousness usually develops at the time of the accident, although the patient may be hospitalized before it occurs [*10*]. It is frequently of short duration but has been known to persist for forty-eight hours [*36*]. Signs of cortical irritation, such as convulsions [*47,52*], restlessness [*13,38*], and irrationality [*36*] are seen occasionally. Amnesia [*63*] or a temporary state resembling decerebrate rigidity [*47*] may be noted. These abnormalities are said to be caused by cerebral anoxia rather than cerebral hemorrhage [*47*]. Loss of motor power with or without loss of sensation has been observed in one or more of the extremities following injury to the spinal cord or peripheral nerves [*3,7,11,35,36,52,64*]. However, in one patient with paraplegia, an exhaustive study including laminectomy, demonstrated no evidence of direct trauma to the spinal cord or vertebrae [*38*]. In this instance the findings were presumed to be due to ischemia of the spinal cord brought about by back pressure and subsequent thromboses in the vessels of the intervertebral venous plexus.

Skeletal. The most common complication of traumatic asphyxia is fracture of the ribs [*5,16,29,30,42,43,47*]. The pelvis [*4,16,34,36,65*], humerus [*36*], clavicle [*54*], radius [*8*], ulna [*34*], femur [*35*], maxilla [*35*], metatarsals [*31*], tibia [*36*], and vertebrae [*35,64,66*] have been similarly affected, but fractures of the skull are rare [*34,59*].

Vital Signs. There is nothing characteristic about the blood pressure, pulse, respiratory rate, or temperature [*43*]. The skin may be cold and clammy [*25,32,41*], the pulse feeble and rapid [*54,62*], and the blood pressure low [*8*], but shock from compression of the thorax alone is not common [*47*]. In the presence of complicating

respiratory infections, etc., marked tachypnea and tachycardia may develop, and the temperature may reach as high as 106°F. [*25*].

Subjective Manifestations. Several articles have given vivid descriptions of how the patient felt while being crushed. The chest of one victim was squeezed, "and seemed as if it would burst; he felt as though 'his eyes were coming out,' and 'that the blood rushed to his head,' and that his face was swelling. His nose began to bleed and he had 'a general sort of choking sensation'; he heard someone call out, but a moment later his ears began to sing, and he felt his head burst; he then knew no more . . . " [*28*]. These remarks are similar to those made by our patient. Another subject "suffered compression to such a degree that he thought his rectum was protruding" [*4*].

Incidence. The true incidence of traumatic asphyxia is difficult to determine, because some cases are never recognized while others are diagnosed but never reported [*4,34*]. Laird and Borman [*35*] saw five patients with traumatic asphyxia over a two and a half-year period after observing more than 32,000 hospital and clinic patients in a mining community. Five of their colleagues in nearby industrial practices saw but two cases of traumatic asphyxia of approximately 75,000 major accident victims. Dwek [*8*] reported one case of traumatic asphyxia of over 18,500 hospital and accident patients in an area with heavy military traffic. It is evident, therefore, that this condition is relatively rare.

Etiology. Various types of crushing injuries to the upper part of the abdomen and/or thorax account for the majority of patients with this condition. The compression is usually anteroposterior or posteroanterior in direction, with the patient between the compressing force and a hard surface. Rarely, the compression may be indirect, as when the victim is doubled up by a force which is exerted upon the shoulders or back, bringing the chest in contact with the thighs and knees ("jackknife" injury) [*38,42,57*].

The weight of the compressing force has not been mentioned often, but values of 16,000 pounds [*46*], 7 tons [*57*], 6 tons [*32*], three and a half tons [*38*], two tons [*50*], 3,000 pounds [*66*], one ton [*67*], and 1,400 pounds (our patient) have been recorded. The pressure on the body of one deep sea diver with traumatic asphyxia was estimated to be eighteen and a half pounds to the square inch [*61*].

The length of time during which the victim's body is compressed is usually between two to five minutes. The shortest period is that reported by Parker [*46*] whose patient was subjected to eight tons of pressure for only a fraction of a second. In most instances maximal pressure is sustained at the moment of injury, but occasionally, as in our patient, the victim may be "squeezed" slowly [*29,57,68*].

In earlier reports the victims were usually crushed to death by other persons when fire caused panic in large theaters [*1,25*]. More commonly traumatic asphyxia is seen in accidents involving automobiles [*4,8,24,30–32,34–36,54,66*], elevators [*13,29,42,43,46,52,68*], airplanes [*8*], trains [*38*], street cars [*5,9*], cow catchers [*27*], hydraulic lifts [*38,63*], wagons [*33,62*], steam shovels [*35*], etc. Some patients have been buried under debris as in mine disasters [*35*], air raid bombings [*26*], or falling masonry [*9*]. It has occurred once in a deep sea diver [*61*], and has been noted in persons who were hanged unsuccessfully [*47*]. This syndrome apparently was produced in one patient who was thrown forcefully to the ground when his bicycle was struck by a wagon [*33*]. In one seventeen-hour old infant with a large unbilical hernia that contained the whole liver, traumatic asphyxia developed after great pressure was exerted on the liver in order to reduce it into the abdominal cavity [*36*]. To this imposing list may be added our patient whose injury by a stationary airplane is unique.

Less pronounced manifestations of traumatic asphyxia have appeared rarely in patients with epileptic seizures [*6,47,53,55,69*], whooping cough [*9,25*], violent vomiting [*8,9*], bronchial asthma [*9*], or following difficult delivery when the parturient [*44,62*] or the newborn [*39*] may be afflicted.

Pathogenesis. The pathogenesis of this condition is not understood thoroughly, but a reasonable explanation is available for most of the manifestations. It is generally believed that following sudden severe compression of the upper part of the abdomen or thorax the intrathoracic pressure rises, the superior vena cava becomes obstructed, and blood from the right side of the heart and great thoracic veins may be forcibly ejected cephalad. (Occasionally during epileptic seizures, severe paroxysms of coughing and vomiting, etc., the same phenomena result from the forceful contraction of the thoracoabdominal muscles against a closed glottis [*6*].) Since the veins in the head and neck and sometimes in the subclavian and axillary regions do

not contain competent valves, blood readily enters these vessels when back pressure suddenly develops. This causes distention of the venules and capillaries, and minute hemorrhages may occur. When the pressure is released, the dilated vessels do not regain their tone quickly [*47*]. The hypoxia which is present during the thoracoabdominal compression may contribute to the paresis of the vessel walls [*31*]. It was suggested that injury to the abdominal sympathetic nerves produced paralysis of the vessel walls in the distribution of the cervical sympathetic nerves. However, this postulate was not confirmed experimentally by the investigators [*36*]. The stagnated blood in the atonic vessels presumably accounts for the persistent bluish discoloration observed clinically [*47*]. In support of this theory, it may be noted that the cutaneous discoloration frequently blanches upon pressure [*24,25,65*] and does not usually undergo the chromatic changes which one ordinarily sees in healing ecchymoses [*4,25,27,38*].

We propose that in some patients congestion of the arterioles may also develop because blood flow to the affected areas is unaltered, whereas drainage of blood from these sites is impaired. This might explain the red discoloration seen initially in our patient and in the one observed by Conwell [*34*].

The distribution of the cutaneous discoloration coincides with the areas supplied by veins with incompetent valves, but one side may be more involved than the other [*33–35*]. This may be due to the difference in length and angulation of the right and left innominate veins, and the fact that in certain cases the compression is unilateral [*34,43*].

It is of interest that the characteristic skin changes have failed to appear under points of pressure such as the collar band [*6,62,69*], hat band [*9,38*], and the suspenders [*36*]. This suggests that if an equal counterpressure is applied to the skin, overdistention of the capillaries and venules is prevented [*31*]. Similarly, the protection afforded by the skull and cerebrospinal fluid probably explains the infrequency of intracranial and retinal hemorrhage. The relative lack of tissue support around the conjunctivas is believed to account for the distribution and extent of hemorrhage in this region.

Experimental Data. The typical picture of traumatic asphyxia has not been reproduced satisfactorily in animals, and this may be due to the difference in structure and dynamics of the animal and human thoraces [*10*]. It was found that sudden or continued compression of the abdomen of rabbits produced dilatation of the veins of the ear without discoloration of the face; also, that division of the splanchnic nerves in the abdomen caused dilatation of the vessels in the skin but no discoloration of the face [*36*]. Perthes [*2*] observed dilatation of the ear veins and cyanosis of the mouth and eyelids following severe compression of the thorax in two white rabbits. Reichert and Martin [*10*] applied heavy iron weights to the upper part of the abdomen and lower part of the thorax of two anesthetized cats until respirations ceased and artificial resuscitation became necessary. This produced a transient and inconstant engorgement of the retinal, conjunctival and sublingual veins, with reddening of the skin overlying the neck, ears and upper part of the chest. These authors then postulated that a damaged liver in traumatic asphyxia might liberate heparin. Therefore, heparin was administered intravenously to an anesthetized dog, and a heavy iron weight was allowed to fall onto the area of the diaphragm. This resulted in blurring of the optic discs, hemorrhage in the retinas, and numerous hepatic lacerations with hemoperitoneum. Another dog was given histamine intravenously, because this substance is known to form quickly in traumatized tissues. Immediately thereafter a heavy weight was placed upon the animal's chest, and a momentary bluish discoloration of the ears and lips developed, and scattered petechiae in the skin were seen. In two other dogs the superior vena cava proximal to the azygos vein was occluded for ten minutes. This produced retinal hemorrhages, dusky conjunctivas, full lingual veins, small hemorrhages in the mucous membranes of the cheeks, pinkish discoloration of the shoulders and head, and weakness of the hind limbs. These abnormalities were still apparent four days later.

Pathological Summary. In 1923 Heuer [*36*] reviewed all previous autopsy data, and little information has been added in subsequent reports [*35,38,39*]. The brain has usually shown no change except cerebral congestion, although subdural hemorrhage was noted once by Ollivier [*1*]. Extensive bloody infiltrations have been observed in various soft tissues of the head and neck. Pulmonary abnormalities have consisted of hemorrhage, edema, rupture of the lung, hemothorax, pneumothorax, bronchopneumonia, fat emboli, multiple abscesses, throm-

boses, and subserosal hemorrhage in the pleura and pericardium. Abdominal lesions have included hemoperitoneum, hernias, and rupture of various viscera. Fractures of the ribs, pelvis, vertebrae, and extremities have been encountered commonly, whereas fractures of the skull have occurred rarely [*1*].

In a few living subjects, pieces of discolored skin from the neck or chest have been removed for microscopic examination. Beach and Cobb [*29*], as well as Winslow [*42*], found marked distention of the capillaries and small veins but no blood was seen outside the vessel walls. Robertson [*25*] noted only perivascular round cell infiltration in the skin of the first patient he examined. In another patient, however, he found blood pigment, hemorrhage, and edema in the deep layers of the corium and subcutaneous fat. Hemorrhage in the tissues around the blood vessels was also reported [*9,36*].

Laboratory Data. A relative paucity of information is available on this aspect of traumatic asphyxia. The blood has been described as being black [*56*] with an increased fluidity [*8*] and bleeding, and coagulation times were normal in one study [*44*]. The icterus index was never elevated during a two months period of observation in one patient [*35*]. The urine is usually non-contributory, but hematuria [*35,36*], albuminuria [*25*], urobilinuria [*35*], and large granular casts [*10*] have been found. The cerebrospinal fluid was xanthochromic and contained a protein of 88 mg. per cent in one patient [*10*], whereas ordinarily the spinal puncture reveals no abnormalities [*25,40*].

The venous pressure, blood urea nitrogen and electrocardiograms in our patient were essentially within normal limits, but the serum transaminase was elevated. Similar investigations in other patients with traumatic asphyxia have not been recorded.

Differential Diagnosis. The diagnosis should be evident from the history and the appearance of the patient. In fact, the victim's appearance is so outstanding that memory alone enabled Shimonek to describe in detail a case that he had seen 25 years previously [*56*]. Nevertheless, any condition which causes obstruction of the superior vena cava may bear some resemblance to traumatic asphyxia [*47*]. Arnold [*70*] reported on a patient with an aortic aneurysm that compressed both internal jugulars but spared the subclavian veins. This led to cyanosis of the face and neck, and proptosis of the eyes. There was also enormous dilatation of the superficial veins of the head and neck, a feature not seen in traumatic asphyxia. The initial clinical impression in our patient was superior vena caval obstruction, but the normal venous pressure in the arms and the chest film that revealed no abnormalities prompted a change in our thinking. Had we known about traumatic asphyxia at that time, the diagnosis would have been obvious.

Young [*40*] and Henry [*58*] claimed that traumatic asphyxia may be confused with basilar skull fractures, because in both conditions there may be subconjunctival hemorrhage, periorbital ecchymosis, epistaxis and bleeding from the ears. However, skull fractures are extremely rare in traumatic asphyxia, since the force of injury is not applied to the head [*34,59*].

Treatment. The treatment is supportive and should be directed toward the associated injuries and complications. Phlebotomy has been performed in two patients, and in each case this procedure was thought to be lifesaving [*13,56*].

Prognosis. This disorder is usually not as serious as the patient's initial appearance would suggest. Approximately 90 per cent of the patients who live for more than an hour will recover [*31,47*]. In the 143 cases collected from the literature by Laird and Borman [*35*], twenty-seven patients were dead upon admission to the hospital or died minutes thereafter. Of the 116 patients who survived the initial injury, 104 recovered, whereas twelve ultimately died. Death results from severe associated injuries or subsequent infection, and these same factors will determine the rapidity and extent of recovery [*16*].

SUMMARY

1. A unique case of traumatic asphyxia is described and a review of the subject is presented.

2. Traumatic asphyxia is a relatively rare but distinct and unforgettable syndrome characterized by striking bluish red to bluish black discoloration of the head, neck, and upper part of the thorax with massive subconjunctival hemorrhage. In the majority of cases it results from severe compression or squeezing injuries to the thorax and/or upper part of the abdomen.

3. The rise in intrathoracic pressure brought about by a crushing injury causes the blood from the right side of the heart and great thoracic

veins to be ejected cephalad. This in turn produces sudden overdistention and paralysis of the cutaneous capillaries and venules in that portion of the body supplied by veins with incompetent valves. Occasionally, minute hemorrhages may also appear in the affected areas, but the discoloration is due primarily to venous stasis and usually clears completely within two weeks without undergoing chromatic changes.

4. Associated injuries and complications are common, especially those affecting the eyes. In addition to the subconjunctival hemorrhage which usually persists for about a month, there may be exophthalmos, swollen lids, pupillary changes, ocular palsies, hemorrhages and exudates in the retina, papilledema, and all sorts of transient or permanent disturbances in vision.

5. Varying degrees of hemorrhage may be present in the mouth, nose and ears, and tinnitus or temporary deafness may develop.

6. Many different pulmonary complications have been encountered, whereas cardiac abnormalities have been recognized rarely. The patient reported on herein is the first to manifest pericardial effusion. It is suggested that a search be made for injury to the heart in every victim of traumatic asphyxia.

7. Unconsciousness, signs of cortical irritation, and injury to the spinal cord or peripheral nerves may be observed, and fractures of various bones, especially the ribs, are very common. Skull fractures, however, are quite rare.

8. Traumatic asphyxia has not been reproduced satisfactorily in animals, presumably because of the difference in structure and function of the animal and human thoraces.

9. Examination at necropsy has served only to confirm the abnormalities noted clinically. It is interesting, however, that the brain has usually shown no change except cerebral congestion. In a few living subjects, biopsies of the skin from the affected areas have demonstrated distention of the capillaries and venules, with or without a very small amount of blood in the surrounding tissues.

10. The diagnosis is made from the all important history and characteristic appearance of the patient.

11. The treatment is supportive and should be directed toward the associated injuries and complications.

12. Traumatic asphyxia is usually not as serious as the patient's initial appearance would suggest. Approximately 90 per cent of those who survive for more than an hour will recover.

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Clinicopathologic Conference

Dysphagia, Melena, Uremia and Hypertension in an Aged Patient

STENOGRAPHIC reports, edited by Lillian Recant, M.D. and W. Stanley Hartroft, M.D. of weekly clinicopathologic conferences held in the Barnes and Wohl Hospitals, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine, Preventive Medicine, and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient was an eighty-three year old white widow who entered Barnes Hospital on February 27, 1959 with the chief complaint of difficulty in swallowing. She gave a history that was considered unreliable.

Two years before admission to Barnes Hospital she had been in another hospital because of dysphagia; esophagoscopy was performed and the patient was subsequently told that there was narrowing of the esophagus. During the year before admission she became weaker. Four or five months before admission she suddenly became unable to walk, and although there was subsequent improvement, members of her family still had to help her each time she left her bed or chair. She thought that in recent months her right arm and leg had become weaker than her left. She continued to have dysphagia. At times food tended to stick at a point below the lower sternum. In addition, she had vague pain in the upper part of her abdomen after meals. This became worse during the month before admission, and as a result she virtually stopped eating. She had severe headaches and painful swelling of the feet, but denied any other symptoms. Her son stated that she had had nocturia, three or four times each night for the three-week period before admission.

Except for lifelong constipation and an episode of pneumonia in the remote past there were no significant facts elicited in the past history. One brother had diabetes. No other familial diseases were present.

On physical examination the temperature was 37.2°C., the pulse 90 per minute, respiration 24 per minute, and the blood pressure, 190/100 mm. Hg. The patient was a pale, elderly white woman who was confused. Her skin was excoriated, inelastic, with poor turgor. On funduscopy, the arterioles were tortuous, but no hemorrhages or exudates were seen. The left border of cardiac dullness was at the midclavicular line in the sixth left intercostal space. A grade 2 systolic murmur was present at the apex. The A-2 was louder than P-2. The lungs were clear, but the breath sounds were distant. No masses or organs were palpable in the abdomen. There was a right inguinal hernia. Varicosities and a trace of edema of the ankles were described. On neurologic examination, one examiner noted slight right facial weakness and slight weakness of right arm and leg when compared to the left. No reflex changes were present.

The laboratory data were as follows: The hematocrit was 29 per cent and the white blood cell count 20,800 per cu. mm. The admission urine had a pH of 5, a trace of protein, and no sugar. On microscopic examination there were ten red blood cells and thirty to forty white blood cells per high power field; red blood cell casts and occasional finely granular casts were seen. The fasting blood sugar was 108 mg. per cent; the non-protein nitrogen was 142 mg. per cent. A barium swallow was interpreted as showing a small esophageal hiatus hernia with esophagitis of the distal thoracic esophagus. Roentgenograms of the chest were interpreted as showing pneumonitis and bronchiectasis of the right middle and lower lobes of the lung with associated disease in the left lower lobe of the lung. In addition, extensive aortic arteriosclerosis and a compression fracture of the first lumbar vertebra were described. An electrocardiogram was interpreted as being compatible with left ventricular enlargement and digitalis effect.

On admission, the patient was given intravenous fluids. Antacids and an ulcer diet were

prescribed, but she took food, liquids, and oral medication very poorly. On the fourth hospital day, esophagoscopy was performed. There was minimal evidence of esophagitis in the distal esophagus. The cardioesophageal junction seemed to be in tight spasm. A No. 22 French bougie was passed into the stomach. A cardiomyotomy was planned if the patient's status would permit. Digitalization was begun.

Studies performed on the sixth hospital day showed that the non-protein nitrogen had risen to 185 mg. per cent; the serum sodium was 126 mEq. per L.; potassium 6.3 mEq. per L.; carbon dioxide combining power 23.6 mEq. per L.; uric acid 10.3 mg. per cent; calcium 8.2 mg. per cent; phosphorus 4.3 mg. per cent; and alkaline phosphatase 4.3 Bodansky units. Only 1 per cent of an injected dose of phenolsulfonpthalein was excreted within one hour.

The patient was disoriented, shouted frequently, and refused to eat or drink. Despite the administration of 2,500 ml. of intravenous fluids in a twenty-four-hour period, her urinary output was only 315 ml. The urine had become grossly bloody.

On the seventh hospital day the blood pressure was 174/76 mm. Hg. The patient appeared to be cachectic. There was evidence of extracellular fluid deficit. The urine contained 2 plus protein, many red blood cells, and a few coarse and finely granular casts. The hematocrit was 27 per cent. Red blood cell indices were normal except for a mean corpuscular hemoglobin concentration of 30 per cent. The white blood cell count was 15,000 per cu. mm. with a normal differential count. Several polymorphonuclear leukocytes had as many as seven lobes. Urine osmolality was 310 mOsm. per L. The stool guaiac reaction was strongly positive.

After intravenous administration of 1 L. of 5 per cent glucose in saline solution there was less evidence of extracellular fluid deficit, although urinary output did not increase. In an attempt to rule out obstruction of the urinary tract, cystoscopy was performed. Findings revealed no abnormalities. Retrograde pyelograms showed a small right kidney without ureteral obstruction. Roentgenograms of the abdomen were believed to show residual barium, sigmoid diverticula, generalized osteoporosis, calcification within uterine myoma, and bilaterally contracted kidneys.

Slow infusion of 50 per cent glucose in water was begun, as was rectal administration of sodium-cycle exchange resins. The urinary output remained less than 250 ml. per day and was usually less than 100 ml. per day. Despite persistence of positive stool guaiacs, the hematocrit was stable between 22 and 25 per cent. The patient continued to be disoriented and weak.

The non-protein nitrogen rose progressively to 201 mg. per cent, the serum sodium ranged between 125 and 130 mEq. per L.; the CO_2 was 21 to 23 mEq. per L. and the serum chloride was 85 to 97 mEq./L. The serum potassium fell from an initial high level of 6.5 mEq./L. to 3.7 mEq. per L. An electrocardiogram was unchanged when compared with the tracing taken earlier. A culture of clean voided urine was sterile.

After the eleventh hospital day, the patient's status alternated between episodes of complete unresponsiveness and disoriented moaning. Despite turning at intervals a sacral decubitus ulcer developed. Suctioning was required to clear the nasopharynx. She became hypotensive on the fifteenth hospital day, and died quietly on the seventeenth hospital day.

CLINICAL DISCUSSION

DR. E. REINHARD: Dr. Margulis, will you discuss the patient's roentgenograms at this time?

DR. ALEXANDER MARGULIS: The esophagus showed tertiary contractions throughout and an area of narrowing in the distal thoracic part. This area had a good mucosal pattern. There was a small hiatus hernia present. Examination of the chest showed a pneumonic process which most likely was chronic, in the right middle lobe of the lung. There was some loss of volume of the right middle lobe, and radiolucencies interspersed with densities surrounding them, were strongly suggestive of underlying bronchiectasis. In addition there was osteoporosis and a fracture of the body of first lumbar vertebra with considerable loss of height. There were hypertrophic changes indicating that this was not a new process. Abdominal examination showed small kidneys. There was extensive calcification in the abdominal aorta. A right retrograde pyelogram, showed the right kidney to be quite small. The calyces were moderately sharply outlined, but we were dealing with a non-functioning kidney with calyces that were only distorted by the general process of shrinking. This was either nephrosclerosis or pyelonephritis or both.

DR. REINHARD: I think we can say at this point that this patient had severe renal disease with small kidneys. She had systolic hyperten-

sion and perhaps mild diastolic hypertension. She had a hiatus hernia. She probably had esophagitis and possible achalasia. Presumably there was severe generalized arteriosclerosis; severe osteoporosis with compression fracture, degenerative arthritis, and a pulmonary infiltrate suggestive of bronchiectasis. Let us begin with this patient's chief complaints on admission, namely swallowing difficulties and gastrointestinal complaints. This patient had dysphagia; she had vague pain in the upper part of the abdomen; she vomited and she apparently belched quite a bit. The patient was admitted to the chest surgery service for the purpose of performing an operation for relief of what was presumed to be cardiospasm with achalasia. It soon became apparent that she was in no condition to have major surgery. Dr. Gieselman, would you discuss the functional disturbance in achalasia? What are the pathologic lesions that cause this functional disturbance?

DR. RALPH GIESELMAN: Achalasia is a term given to a clinical syndrome characterized by the symptom of dysphagia. The esophagus, on roentgenographic examination, presents a markedly dilated appearance with absence of primary and secondary peristaltic waves. There is also an absence of relaxation of the physiological sphincter of the cardia. The most universal finding in people with achalasia is an absence of, or abnormality of the ganglion cells that constitute Auerbach's plexus in the submucosa of the esophagus.

DR. REINHARD: Was the basic difficulty, spasm of the sphincter?

DR. GIESELMAN: No sir. The trouble was failure of relaxation on deglutition, rather than actual spasm.

DR. REINHARD: It was said that this patient had dilatation performed. Do you think she really had a clinical syndrome that we could call achalasia?

DR. GIESELMAN: Apparently the chest surgeons entertained no doubt that that was what she had, and what she needed was a cardial myotomy, but the operation was not performed, because her physical condition obviously would not permit it. I must say, I did not see any very good evidence in the protocol to substantiate this diagnosis. There was nothing on the roentgenograms to suggest this lesion. Do you have any comments, Dr. Margulis?

DR. MARGULIS: I would agree with Dr. Gieselman. This did not look like achalasia. This was an esophagitis, the cause of which I do not know.

DR. REINHARD: Dr. Shatz, which if any, of this patient's symptoms do you think we might have attributed to the small esophageal hiatus hernia?

DR. B. SHATZ: We know that in patients who have esophageal hiatus hernias, the cardia becomes incompetent so that the gastric contents regurgitate back into the lower esophagus and produce an inflammatory reaction in the lower esophagus. Esophagitis is not an uncommon complication of hiatal hernia. The most likely explanation for the patient's esophageal symptoms seemed to me to be esophagitis. The only thing that bothered me on looking at the x-ray films is that the mucosal pattern appeared relatively intact. Most of the changes here were due to the neuromuscular activity of the esophagus, the contractions which we saw were markedly abnormal. They were irregular, and uncoordinated, so that one could think of a neurologic lesion, either local or resulting from cerebral vascular disturbance. Occasionally we see elderly people in whom dysphagia develops and who also have evidence of disturbances in the central nervous system. At autopsy or at operation, nothing is found in the esophagus because all the disturbances are of a functional type, not of a morphologic type.

DR. REINHARD: Patients who have hiatus hernia very often bleed. The mechanism of this bleeding is peptic esophagitis with ulceration. Do you think we can account for this patient's strongly guaiac positive stools, on the basis of what we saw in the esophagus?

DR. SHATZ: This is a possibility but there is another good explanation. This patient had uremia, and we know that erosions of the gastrointestinal tract are very common in uremia.

DR. REINHARD: Dr. Berg, can you think of any primary specific disease of the nervous system to which this esophageal difficulty might be secondary?

DR. LEONARD BERG: No. It is my understanding that esophageal difficulty due to central nervous system disease should effect the upper portion of the esophagus, where there is striated muscle in the wall rather than the lower portion of the esophagus which is not so dependent on the central nervous system. Dysphagia of course, is a frequent complaint in neurologic disease both involving muscle itself, the lower motor neuron, the cranial nerve nuclei in the brain stem as well as descending cortical bulbar

fibers. In this patient, I believe that the nervous system was not primarily involved, if we can exclude Auerbach's plexus in the esophageal wall.

DR. REINHARD: Dr. Gieselman, do you think we should consider any causes for gastrointestinal bleeding other than uremia and esophagitis secondary to hiatus hernia?

DR. GIESELMAN: We are not given any good clues that would lead us to consider anything further. She could have had an inapparent gastric ulcer, associated with her poor nutrition or the uremic state.

DR. REINHARD: Dr. Margulis, one of the rare causes of dysphagia is scleroderma with involvement of the esophagus. There was nothing to suggest scleroderma of the skin of the face or hands in this case. What are the roentgenographic manifestations of scleroderma involving the esophagus?

DR. MARGULIS: Scleroderma results in a failure of normal propulsion of food in the esophagus. The peristalsis is disturbed, and this is easily demonstrable when you have the patient examined in the recumbent position. Esophagitis in the lower portion of the esophagus is quite frequent, and ulcers are not uncommon.

DR. REINHARD: Do you think this is something we ought to consider, Dr. Gieselman?

DR. GIESELMAN: From the roentgenographic standpoint, no.

DR. MARGULIS: You usually do not get tertiary contractions. You usually get a tonic flabby esophagus.

DR. REINHARD: In the absence of any confirmatory signs of scleroderma elsewhere I think we certainly can go no further, except to put this down as a very unlikely possibility.

One last category of disease needs to be discussed in connection with dysphagia and esophageal inflammation. Dr. Shatz, is it possible that the patient had mediastinal disease, either neoplastic or inflammatory with secondary esophageal involvement?

DR. SHATZ: This is possible, but I don't think we have any evidence for mediastinal disease. The patient had bronchiectasis, and if this were in any way related to the esophageal disease, I would say that the pulmonary situation could have been a complication of prolonged or intermittent esophageal obstruction with aspirations. However, this is not the usual area of the lung involved.

DR. REINHARD: Let us now examine the problem of the renal lesion. Dr. Kime, when progressive renal failure develops in a patient without a history of known renal disease, it is always difficult and often impossible to determine the etiology of the renal disease. In this particular case, did we have any hint that would suggest the nature of the basic underlying disease?

DR. WESLEY KIME: The case for the presence of renal disease which may have existed before the onset of renal failure was based largely on the roentgenographic finding of moderately small kidneys. It was not possible to arrive at a specific diagnosis from this finding alone. However, it was possible to rule out certain diagnoses. Thus, polycystic disease was unlikely. Amyloidosis and the collagen diseases were not likely, for most of these renal conditions are considered "infiltrative" and are usually associated with normal size or even large kidneys, although progression of these diseases may eventually result in kidneys of less than normal size. Moderately small kidneys are consistent with chronic glomerulonephritis, pyelonephritis and nephrosclerosis. There are no data from the history which would be helpful in further differentiation. Laboratory data are somewhat more helpful. The retrograde pyelograms were consistent with pyelonephritis but there was less calyceal distortion than usually expected in advanced or severe pyelonephritis. Severe pyelonephritis, however, may exist in the absence of marked roentgenographic changes. The finding of numerous white cells in one urinalysis was consistent with pyelonephritis, but this finding may occasionally be noted in other conditions.

Moderate hypertension, which was present in this case, is no more helpful than kidney size in arriving at a specific etiologic diagnosis.

The paucity of data leading to a specific etiologic diagnosis of the renal condition associated with the small kidneys was not unusual, particularly in elderly people who forget events that may have happened years previously or who may not have been impressed by those events. Furthermore, it is now thought that pyelonephritis may be asymptomatic for many years.

It should be stated that the underlying renal disease, whatever its exact etiology, may have had nothing to do with the renal failure which contributed to the death of the patient.

DR. REINHARD: Dr. Morrin, it seems to me that as far as the terminal progressive azotemia

was concerned there were the following three possibilities in this patient: (1) an exacerbation of chronic renal disease; (2) a superimposed acute renal disease of a different type; or (3) the progressive azotemia was due to extrarenal factors in a patient with underlying chronic renal disease. What do you think about these three possibilities?

DR. PETER MORRIN: This patient almost certainly had nephrosclerosis, and I will be very surprised if she did not have some chronic pyelonephritis. However, a significant symptomatic renal history only extended over a three- to four-week period with the onset of nocturia. If her nephrosclerosis or chronic pyelonephritis had evolved gradually to the level of high grade renal failure with which she had presented, one would expect a longer symptomatic period. Therefore, I am inclined to postulate the superimposition of some subacute event. Regarding the superimposition of a third disease besides nephrosclerosis or chronic pyelonephritis, the finding of red cells is disturbing to me. First may I say that I am a little skeptical if red cell casts were really present. They were not found on the medical service, where the urine was examined very carefully, and in most conditions where red cell casts are found you do not expect them to be present at the onset of the disease and to disappear while the renal disease continues with unabated severity. Therefore, I think we must question the presence of these red cell casts. However, if they were present we can not exclude a diagnosis of acute glomerulonephritis. I personally am not inclined to favor this diagnosis, but we must mention it. A re-exacerbation of acute pyelonephritis would statistically be the most common cause of renal failure in a woman of this age group. Against this we have no evidence of bacterial infection on culture, and the white cells in her urine decreased in number while she was in the hospital and white cell casts were not found on any occasion. Although I think the patient had some pyelonephritis, I do not believe that acute exacerbation of this disease was responsible for her renal failure. She was certainly dehydrated when we saw her on the ward and in a patient with chronic renal disease, dehydration is tolerated much more poorly than in a patient with normal kidneys. If dehydration is severe enough, it can go on to produce acute tubular necrosis, and there was nothing in this woman's history that enabled me to rule out the diagnosis of acute tubular necrosis. Finally, I think we have to consider the possibility of renal infarction. This woman had severe hematuria late in the course of her disease, which would be uncommon in acute tubular necrosis, but would be quite consistent with renal infarction, either arterial or venous. Other features of venous infarction were not present, but I will not be at all surprised if she did have some arterial infarction.

DR. REINHARD: Some of the extrarenal factors, which may produce or contribute to renal failure are the following: vomiting, diarrhea, acute infection, congestive heart failure, diabetic coma, Addison's disease, alkalosis, the hepatorenal syndrome and gastrointestinal hemorrhage. The patient certainly had gastrointestinal hemorrhage; she had been vomiting before she came into the hospital. I wonder, Dr. Kime, if there is any reason to suspect any of these other disorders as contributing to her terminal renal failure?

DR. KIME: There is no convincing clinical data for any of the possible causes which you have listed.

DR. REINHARD: Dr. Kime, I wonder if you would discuss the mechanism by which decreased renal blood flow and hyponatremia play a role in so-called prerenal azotemia?

DR. KIME: It is customary to emphasize decreased renal blood flow in the pathogenesis of azotemia of prerenal origin, but renal blood flow *per se* is not the vital factor. Nitrogenous products are normally excreted only by filtration; thus, it is only when glomerular filtration rate is decreased with the retention of nitrogenous substances that azotemia occurs. However, a decrease in renal blood flow may not necessarily result in obligatory reduction of filtration rate. Some extrarenal conditions which may be associated with reduced filtration rates are congestive heart failure, hypotension, and decreased extracellular fluid volume. The resulting azotemia may be more striking if any of these prerenal factors are superimposed on pre-existing renal parenchymal or vascular disease.

In the past it was stated that hyponatremia or decreased plasma concentration of sodium caused renal insufficiency or even failure. It is now thought that this statement is an oversimplification at best. Isotope studies have demonstrated that decreased plasma sodium concentration may exist in the presence of

increased or normal as well as decreased total body sodium. Irrespective of the absolute quantity of total body sodium, hyponatremia would occur if the proportion of extracellular water to sodium is greater than normal. The sodium concentration is thus seen to be merely an expression of the ratio of sodium to water, not a direct indication of the absolute quantity of total body sodium. Hyperglycemia may cause transfer of cellular water to the extracellular compartment and result in hyponatremia. It has been proposed that the usual extracellular sodium and intracellular potassium concentration gradients might be reversed in some debilitated states while total body amounts of these elements remain normal. Some have proposed that this reversal may result in hyponatremia, but there are theoretical reasons for doubting that hyponatremia is the direct result of such a mechanism. In the presence of severe lipemia the concentration of sodium per liter of plasma water may be normal although the concentration per liter of plasma may be low; this is spurious hyponatremia. Thus the term "hyponatremia" is not meaningful unless there is also consideration of total body sodium and water and compartmental shifts. It should also be noted that hyponatremia from any cause does not necessarily indicate plasma hypotonicity if concentrations of other solutes are high. Hyperglycemia may be associated with hyponatremia, yet the plasma may possess a greater than normal effective osmolality. High concentrations of plasma urea (as in uremia) may result in greater than normal plasma osmolality, but because urea freely enters most fluid compartments, there is no change in effective osmolality.

Hyponatremia *per se* may or may not be associated with renal insufficiency. In the severe hyponatremia of advanced tuberculosis, renal insufficiency is not the rule. Moreover, when hyponatremia and renal insufficiency (manifested by azotemia) coexist, a cause and effect relation does not necessarily follow. Congestive failure appears to be an excellent example of the unrelated coexistence of hyponatremia and azotemia. Some factor, most likely associated with altered hemodynamics, results in decreased filtration rate, even though there may be no intrinsic renal parenchymal disease. Meanwhile, the complex of factors known as the volume control mechanism responds to congestive failure by increased activity which effects the kidney as well as other organs. The kidney is made to conserve both salt and water. This is accomplished primarily by tubular mechanisms largely through hormonal control, although the decreased filtration rate caused by congestive failure and the resulting reversed glomerular-tubular balance may be contributory. Vigorous treatment with mercurials or chlorothiazide therapy will result in isotonic loss of water and solute, since these diuretics apparently exert their action on the proximal tubule. Unless the congestive failure is alleviated, however, the volume control mechanism continues to act, one of its actions being the stimulation of thirst. If water without solutes is allowed *ad libitum*, hyponatremia is the inevitable result. Thus hyponatremia is the result of one effect of congestive failure, the abnormally active volume control system, and azotemia the result of quite another, the hemodynamic effects of decreased cardiac output upon glomerular filtration rate. As congestive failure becomes more severe, both of these factors will result in more striking alterations, so that hyponatremia and azotemia usually increase together. At this stage, if the physician attempts to treat the renal failure by treating the supposedly causal hyponatremia with hypertonic saline solutions, congestive failure, with its attendant abnormalities is frequently made worse. On the other hand, filtration rate in congestive failure may be decreased while the plasma sodium concentration remains normal.

DR. REINHARD: Dr. Morrin, you saw this patient while she was on the medical ward. I wonder if you would discuss the problems that existed in her management?

DR. MORRIN: This patient presented a rather perplexing problem. Because we did not have a good history of urinary output and because she was incontinent, we were obliged to insert an indwelling catheter to obtain an accurate urine output, although this is contrary to our usual practice. We believed that it was essential to rule out dehydration as a cause of oliguria. She was rehydrated with 1 L. of glucose and saline. During this time there was no increase in her urinary output, although she was clinically improved by rehydration. We concluded, therefore, that she had acute renal failure which was no longer explicable on the basis of dehydration alone. She was started on a regimen for acute renal failure with restriction of fluids to approximately 400 cc. per day, plus a volume equal to her output of urine. This was given continuously

as hypertonic glucose by intravenous catheter. The other possibility that we could not exclude, owing to the vague and unreliable history, was acute obstruction of the urinary tract. Cystoscopy and retrograde pyelography were therefore performed on one side. The patient had renal failure which we believed to be acute or subacute and there was bilateral renal disease which must have involved all of her functioning nephrons, and which had to be on a parenchymal level in the kidney or on a vascular level proximal to the kidneys.

DR. REINHARD: Let us consider this patient's blood pressure. During the first five days she was in the hospital, her blood pressure averaged about 200/95 mm. Hg. During the next seven days her blood pressure was 160/70 mm. Hg, and terminally she was periodically hypotensive. I will assume that this patient's elevated blood pressure can be accounted for by advanced arteriosclerosis. Dr. Perry, do you think that there is any reason to believe that there was increased peripheral vascular resistance not accounted for by arteriosclerosis?

DR. MITCHELL PERRY: Well, whether or not she had hypertension depends on your definition of hypertension, but I don't really think that this played any significant part in her death.

DR. REINHARD: One question about the lesion in the lung, Dr. Margulis. Do you think this lesion was compatible with a pulmonary infarct? The possibility of renal infarction has been mentioned. The possibility of pulmonary infarction crossed my mind.

DR. MARGULIS: I would say that this most likely was not an infarct, but was an old shrunken, middle lobe with chronic pneumonitis and bronchiectasis.

DR. REINHARD: Dr. Harrington, there were a few blood changes that we could not explain. This patient had a description of her blood smear, that stated that some of the red blood cells were macrocytic. It was also stated that there was hypersegmentation of the polymorphonuclear leukocytes. This patient also had difficulty walking and her feet pained her. Do you think it is conceivable that she had pernicious anemia with macrocytosis masked in part by the bleeding, or by the azotemia?

DR. WILLIAM HARRINGTON: Hypersegmentation can be seen rarely in an iron deficiency but, of course, is much more consistent in the deficiency disease with a megaloblastic marrow. I think that one can say that this patient probably had either B_{12} or folic acid deficiency. Whether or not it played any significant role in her total disease is another matter. I would like to add something that John Vavra pointed out to me. I do not believe he was able to get here. He was attracted by the possibility that this patient had a form of amyloid, often seen with a malabsorption syndrome.

DR. REINHARD: I must say that I had also thought of the possibility of amyloidosis. Primary amyloidosis does occur commonly in very elderly people. I could not, however, find much support for this diagnosis. Can you think of anything to support this diagnosis?

DR. HARRINGTON: The patient had a possible neuropathy. She had dysphagia which is a common feature of the illness. However, she did not have frank intractable heart failure.

DR. REINHARD: Dr. Berg, this patient was mentally confused throughout her stay in the hospital. At times she was totally disoriented. She shouted frequently; she was very difficult to manage. One assumes, at least at first glance, that this was due to the uremia with the associated changes in the blood chemistry. Do you have any reason to believe the patient had any other explanation for her mental confusion?

DR. BERG: No. Even though she had a number of other neurologic symptoms such as severe headaches, the hemiparesis and the vomiting, neurologic disease is unlikely. One thought that did cross my mind very briefly was that this syndrome in the presence of old lung suppuration may mean a brain abscess. It might also mean metastatic disease to the brain, but there really is nothing here to indicate this strongly.

DR. REINHARD: Let us consider the symptom of painful feet. Do you think this patient might have had a peripheral neuritis, and if so, what would this be due to?

DR. BERG: There may be a minimal peripheral neuritis. There were certainly no signs of peripheral nerve deficit. When this happens in an elderly woman, who is extremely malnourished, we really do not have to look very much further. Of course, a B_{12} deficiency or peripheral neuropathy of carcinoma, might be mentioned, but there is not enough evidence here for me to come to that conclusion.

DR. REINHARD: Would anybody else like to make any suggestions here? If not, I will present my final diagnoses. Advanced generalized arteriosclerosis; renal disease, chronic, severe nephrosclerosis with a possible renal infarction

terminally; a small hiatus hernia; esophagitis; osteoporosis, degenerative arthritis. I was attracted by the possibility that this pulmonary infiltrate might have been due to embolic disease, but I think perhaps in view of what Dr. Margulis has said, that this is not true. There is certainly always a possibility in occasions like this that an occult cancer could have been found, but there was really nothing to support this, and one therefore can not make such a diagnosis.

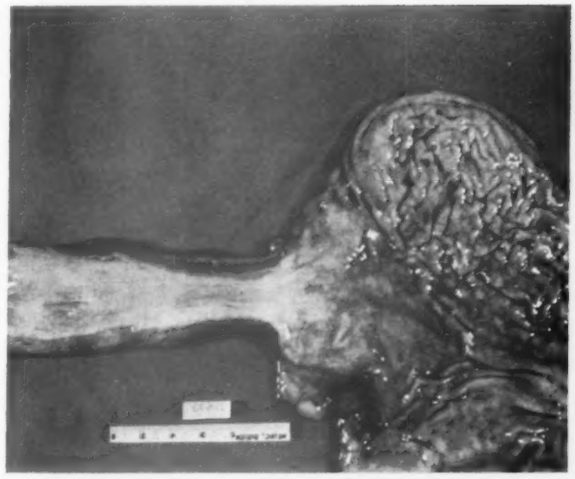


FIG. 1. Gross photograph of the stomach and esophagus. A fusiform narrowing is apparent in the distal third of the esophagus. There is dilatation and hypertrophy of the proximal esophagus.

PATHOLOGIC DISCUSSION

DR. KISSANE: External examination of this aged, poorly-nourished woman revealed the edema described clinically. There was a small amount of serous fluid in each pleural cavity. The epicardial surface showed a moderate fibrinous exudate. The heart itself weighed only 210 gm. There was advanced, but non-occlusive coronary arteriosclerosis. Small recent infarcts were present in the spleen, otherwise there were no abnormalities. The kidneys weighed 71 and 74 gm. They were small and firm. The gross architectural pattern of the kidneys was not markedly distorted. The cortical surfaces were finely granular. There were no infarcts in the kidneys. In the lower third portion of the esophagus, there was a fusiform area that narrowed with moderate dilatation and hypertrophic thickening of the muscularis proximally. (Fig. 1.) The mucosa of the esophagus and stomach was intact. The jejunum contained a number of diverticula between the leaves of the mesentery which is the typical location for small intestinal diverticula. The mucosal surface of the colon bore several patches of fibrinous exudate with a hyperemic border.

Microscopically, the kidneys revealed marked sclerotic thickening of arterioles and small arteries. In consequence of this long-standing degenerative process, the renal parenchyma was conspicuously atrophic and showed marked interstitial fibrosis with a sparse cellular infiltrate, chiefly of mononuclear cells. Glomeruli revealed only non-specific thickening of basement membranes. (Fig. 2.)

A different process of a more recent onset was evident in the small muscular arteries of the kidneys. (Fig. 3.) Many vessels of this size in the kidneys were obliterated by organized thrombi. Arterial walls were frequently discontinuous and evinced considerable adventitial fibrosis. More acute expressions of this process were evident in many of the organs. In the myocardium (Fig. 4) a small muscular artery was the site of very florid necrosis extending through all layers of the wall. The necrotizing process was rather segmental in distribution with foci of nearly complete destruction of the wall. The inflammatory reaction consisted of neutrophils and occasional eosinophils.

In the psoas muscle, a muscular artery showed acute circumferential fibrinoid necrosis with marked advential inflammation and fibrosis. (Fig. 5.) Similar lesions were seen in arteries of the mesentery, jejunum, colon (Fig. 6), the uterus (Fig. 7), and trabecular arteries of the spleen. It was possible to find a practically continuous spectrum of lesions ranging from acute fibrinoid necrosis to more chronic lesions with fibrinous scarring in and about the arterial wall, and thrombi in varying stages of organization in the lumina.

Microscopic examination of the esophagus, in an effort to explain the patient's presenting symptom of dysphagia, revealed two types of lesions. In the connective tissue about the esophagus were several small arteries involved in the acute necrotizing process present elsewhere. (Fig. 8.) There was a marked inflammatory reaction in the continuous esophageal musculature. We believe this process could account for the recent dysphagia on the basis of spasm or impaired muscular contractility. In the esophagus, the vascular lesions were all acute; none seemed old enough to explain the

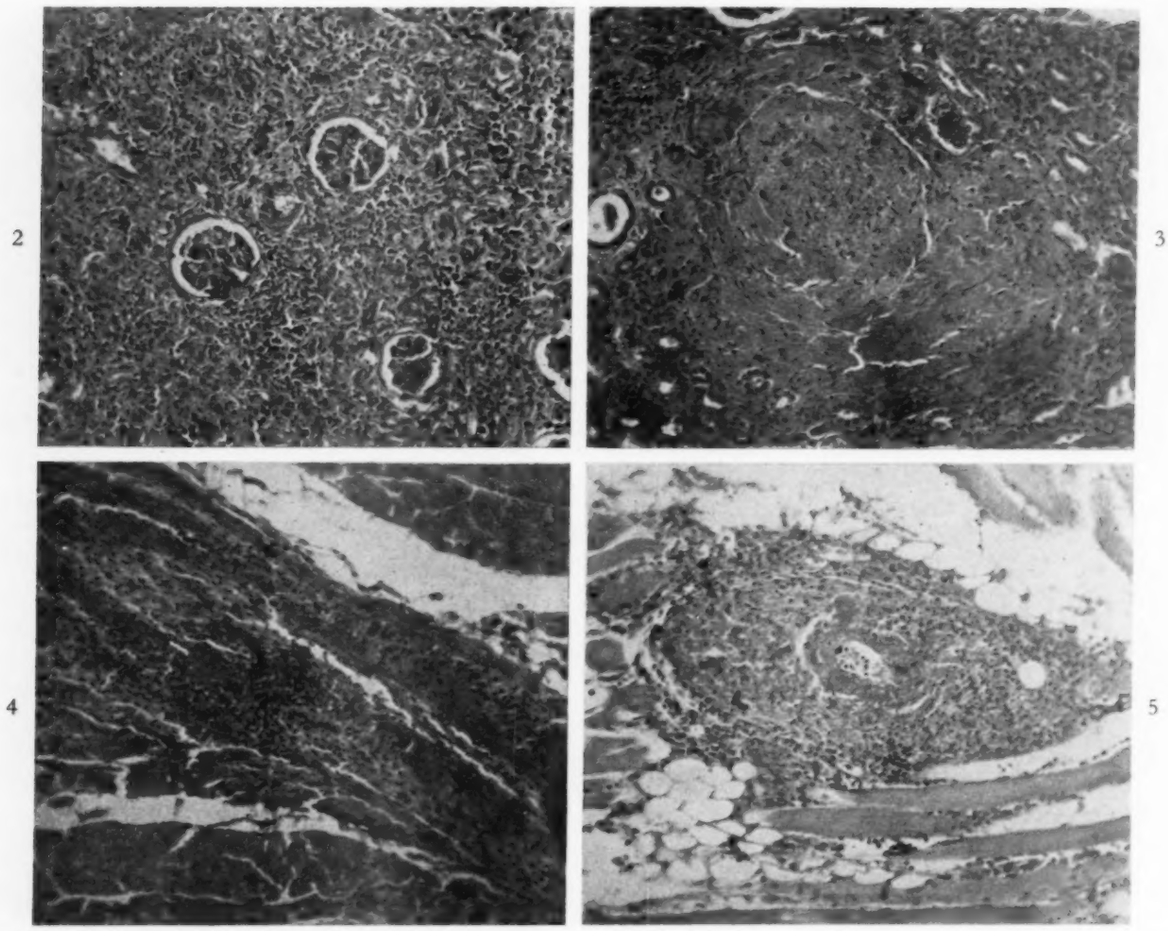


FIG. 2. Photomicrograph showing tubular atrophy interstitial fibrosis, and basal inflammatory reaction. Hematoxylin and eosin × 45.

FIG. 3. Photomicrograph of a muscular artery in the kidney showing almost completely organized thrombus in the lumen, discontinuity of the wall and adventitial fibrosis. Hematoxylin and eosin, magnification × 90.

FIG. 4. Photomicrograph of an artery in the myocardium showing segmental acute necrosis. Hematoxylin and eosin, magnification × 90.

FIG. 5. Photomicrograph of an muscular artery in the psoas muscle showing acute fibrinoid necrosis and marked adventitial inflammatory reaction. Hematoxylin and eosin, magnification × 110.

two-year history of dysphagia. In the musculature of the distal esophagus, however, was another peculiar lesion. The muscular layer here contained multiple discrete nodules which consisted of whorls of plump, fusiform smooth muscle cells. (Fig. 9.) Sections at many points in the circumference of the esophagus demonstrated that these were clearly discrete nodules and not anomalous constricting bands of hypertrophied circular muscle. We have diagnosed these anatomically as multiple leiomyomatous nodules, but could not find any reports of such lesions in cases of cardiospasm. There were, incidentally, normally distributed intrinsic ganglia in the esophagus.

In summary then, this was an elderly woman with long-standing and, judging from the small heart, relatively benign renal disease on the basis of arterial and arteriolar sclerosis. During the last few months of her life, a widespread necrotizing arteritis developed which terminated in renal failure in which she died. In view of the varying ages of the lesions in various organs, the striking involvement of the genitourinary and gastrointestinal systems, and confinement of the lesions exclusively to muscular arteries, we interpreted this as polyarteritis nodosa rather than hypersensitivity angiitis.

The patient had also suffered from dysphagia for at least two years. At autopsy the esophagus

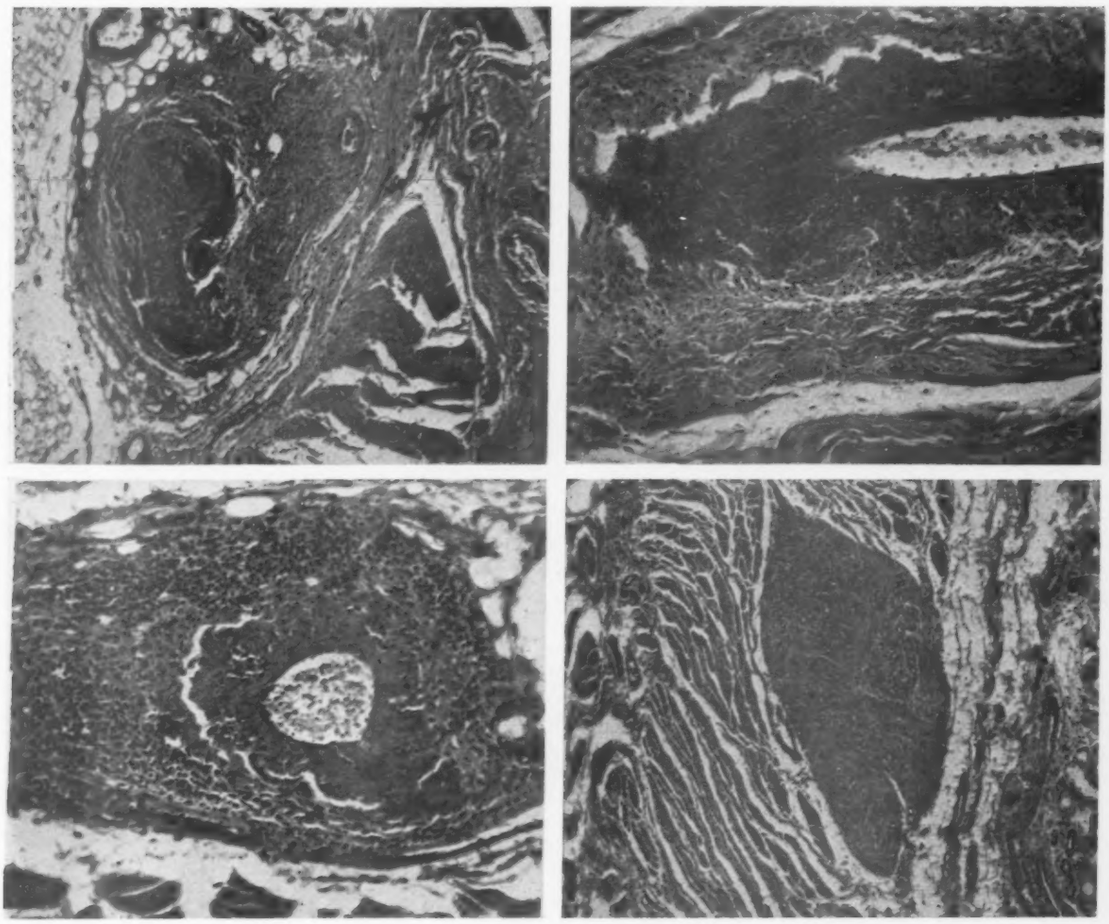


FIG. 6. Photomicrograph of a medium sized artery in the mesocolon showing an aneurysmal dilatation of the arterial wall containing a partly organized thrombus. Hematoxylin and eosin, magnification × 40.

FIG. 7. Acute fibrinoid necrosis of an artery in the cervix uteri. Hematoxylin and eosin, × 100.

FIG. 8. Acute fibrinoid necrosis of a muscular artery in the esophageal muscularis. Hematoxylin and eosin, magnification × 90.

FIG. 9. Circumscribed lentiform nodule of smooth muscle cells in the esophageal muscularis. Hematoxylin and eosin, magnification × 40.

revealed acute arterial necrosis and also multiple leiomyomatous nodules in the muscularis.

Final primary anatomical diagnoses were: acute necrotizing arteritis of the small arteries of the kidneys, heart, esophagus, gastrointestinal tract, spleen, uterus, bone marrow, muscle and periadrenal tissue; partially healed arteritis of arteries of the kidneys and spleen; fibrinous adhesive pericarditis (history of uremia for at least three weeks); recent infarcts of the spleen; arterial and arteriolar nephrosclerosis; pleural effusion, right side 350 cc., left side 300 cc.; pitting edema of lower extremities (3 plus); edema of lungs; bronchopneumonia of lower lobe of the left lung (severe) and of lower lobe of the right lung (slight); slight narrowing of the lower third portion of the esophagus, and hypertrophy of the muscle coat (history of achalasia of the esophagus); multiple small myomatous nodules of lower esophageal wall in addition to acute arteritis.

DISCUSSION

DR. REINHARD: Dr. Kissane, are the findings in the vessels of the heart typical of polyarteritis? We usually think of these as involving larger vessels or are these lesions more consistent with those of hypersensitivity angiitis which leads to rapid renal failure?

DR. KISSANE: We believe that this is polyarteritis nodosa. The disease appeared to be

confined to arteries of the size of muscular arteries. There was no involvement of capillaries; no glomerulitis; and no involvement of veins. The organ distribution of the disease here was typical of polyarteritis. Involvement was conspicious in the intestinal tract and genitourinary system. There were lesions in the ovaries, with sparing of the lungs and brain. Involvement of the spleen, if it occurred, involved capsular arteries and not small arterioles. Evidence was present of a sequence of age of lesions from acute to some partially healed vessels. We did not find frank aneurysms, but they may be hard to find without serially sectioning a number of vessels.

DR. SHATZ: Were the diverticula in the small bowel large enough or extensive enough to have contributed to something like a blind loop syndrome?

DR. KISSANE: I really doubt it. They were 0.5 cm. pouches opening into the small bowel.

DR. REINHARD: Was intestinal bleeding solely a manifestation of uremia?

DR. KISSANE: Uremia plus. Some of the lesions in the colon were on a vascular basis with underlying necrosis.

DR. BERG: Was there normal myenteric plexus in the esophagus?

DR. KISSANE: We found ganglion cells in the esophagus.

Case Reports

Pancreatic Islet Tumor with Severe Diarrhea*

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A patient with persistent watery diarrhea, dehydration, potassium depletion and peptic ulcer associated with a pancreatic islet adenoma was described by Priest and Alexander [*1*] in 1957. In 1958 Verner and Morrison [*2*] described two patients with islet adenomas and chronic diarrhea in whom no peptic ulceration occurred. Both patients died of renal failure secondary to dehydration and potassium depletion. In their review of the literature the latter authors collected seven additional case reports of non-insulin-secreting islet adenomas in which diarrhea was a prominent symptom.

The purpose of this paper is to present a third patient with pancreatic islet tumor, severe diarrhea and potassium depletion in whom peptic ulceration was not a problem. This is thought to be the first reported instance in which the diagnosis was made preoperatively and verified at laparotomy. Successful removal of the tumor resulted in relief of all symptoms.

CASE REPORT

In June 1957, a sixty-year old white woman began to have episodes of anorexia, nausea, vomiting and diarrhea with as many as six or seven watery stools daily. During the first year after the onset of symptoms she was hospitalized four times, usually because of intractable vomiting and dehydration. Her weight fell gradually from 63 to 44 kg. and she had nocturia. Ultimately, severe muscular weakness developed, and she began to be incontinent of feces. The history was non-contributory except for several occurrences of infection of the urinary tract and an episode of possible ureteral colic in 1956.

The significant physical findings were limited to an appearance of dehydration, poor skin turgor, a palpable liver and, at times, slight hypotension. The results of many diagnostic studies were negative. These included several barium enemas and proctoscopic examinations, urinary 5-hydroxyindoleacetic acid tests, a twenty-four–hour urinary 17-ketosteroid and 17-hydroxycorticoid determination, serum protein, amylase, lipase, and protein-bound iodine estimations and liver function tests.

Hypokalemia was first noted in December, 1957, and regularly thereafter. Hyponatremia, acidosis and azotemia developed later. These abnormalities are recorded in Table I. A urinary specific gravity greater than 1.013 was not observed at any time, even during periods of severe dehydration. On repeated examination the urine usually was acid and contained a trace of protein and a moderate number of pus cells and large epithelioid cells. Phenolsulfonphthalein excretion was 53 per cent in two hours when the patient was well hydrated. A pitressin test revealed a maximum specific gravity of 1.009 of a urine specimen collected from 90 to 150 minutes after the subcutaneous injection of 10 (surgical) units.

Several upper gastrointestinal roentgenographic examinations were made, and there was an equivocal finding of an extrinsic pressure defect of the stomach. Many examinations of the feces were performed, but the results, except for an occasionally positive test for occult blood, disclosed no abnormalities. Repeated culture of feces showed no pathogens. The results of oral glucose tolerance tests and of tests of digestion and absorption utilizing d-xylose and I^{131}-labeled fat are given in Table II. No evidence of impaired digestion or absorption was obtained, the results of the d-xylose test being consistent with impaired renal function [*3*] and inconclusive so far as malabsorption is concerned. The results of careful examinations of the feces for fat were repeatedly negative.

Persistent hypophosphatemia was present, associated with slightly elevated values of serum calcium. (Table III.) The serum alkaline phosphatase was normal, and Sulkowitch's test showed no increase in the concentration of urinary calcium. The lamina dura were intact.

In July 1958, after the fifth hospitalization for correction of dehydration and potassium depletion,

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TABLE I
LABORATORY DATA

Hospital Admission	Date	Hemoglobin (gm./100 ml.)	Serum Sodium (mEq./L.)	Serum Potassium (mEq./L.)	Serum Chloride (mEq./L.)	Serum Bicarbonate (mEq./L.)	Blood Urea Nitrogen (mg./100 ml.)
1 to 4	9/57 to 6/58	12 to 14	136	1.8 to 2.9	93 to 111	...	7 to 14
5	7/10/58	17	125	2.2	99	21	49
	7/17/58			3.0	...	13	14
6	9/ 3/58	18	130	4.1	109	7	27
	9/ 5/58	...	130	2.6	...	3	...
	9/ 8/58	...	128	2.4	...	19	94
	9/12/58	10	129	3.3	...	38	20
	9/18/58	...	120	3.4	...	22	...
7	10/13/58	12	125	4.7	...	18	18
8	10/23/58*	14	120*	2.1*	92	18	10
	10/24/58	...	133	2.1	98	23	
	10/26/58	14	135	3.3	102	18	...
	11/ 6/58	...	140	3.6	105	24	(11/25) 14
	2/24/59	12	142	5.1	...	25	...

* Urinary sodium 44 mEq. and potassium 7.9 mEq. per twenty-four hours.

the patient was discharged on a regimen of prednisone, 5 mg. four times daily, and potassium, 125 mEq. daily. On this regimen the diarrhea improved considerably. However, edema developed, and on August 31 the dosage of prednisone was reduced to 5 mg. daily. She became quite weak and anorectic and vomiting recurred. The diarrhea grew much worse. On September 2, dysphagia developed, accompanied by constant pain in the upper abdomen radiating to the back and made worse every time the patient breathed. The vomitus began to contain "coffee grounds" material, and melena was noted.

Examination revealed an acutely ill, disoriented, markedly dehydrated woman. The temperature was 35.5°c., the pulse rate 104, the respiratory rate 26. The systolic blood pressure was 90 mm. Hg by palpation. Laboratory studies (Table I) revealed hemoconcentration, hyponatremia, acidosis and azotemia. Administration of intravenous fluids and hydrocortisone was begun, and corticotropin was injected intramuscularly. She was given 90 mEq. of potassium daily. Within twenty-four hours the vital signs had returned to normal except for tachycardia. After forty-eight

TABLE II
TESTS OF DIGESTION AND ABSORPTION

Observation	Date	Hours after Test Meal						
		Fasting	1	2	3	4	5	6
I^{131}-Labeled Fat Assimilation Tests								
Plasma radioactivity (per cent dose/total plasma volume; normal more than 8 per cent at five and six hours)	6/11/58	...	...	...	...	...	20.4	16
	9/29/58	...	...	...	...	...	9.1	8.4
Oral Glucose Tolerance Tests								
Blood sugar (mg./100 ml.)	3/15/58	96	157	175	160	80	...	...
	6/ 5/58	112	219	152	105	98	...	...
D-Xylose Absorption Tests								
Blood pentose (mg./100 ml.; normal range 25 to 50 mg.)	6/ 9/58	...	...	56	...	...	...	...
	7/21/58	...	...	65	...	...	...	...
Urinary pentose (gm./five hours; normal more than 4 gm. per five hours)	6/ 9/58	...	...	...	...	...	3.2	...
	7/21/58	...	...	...	...	...	0.7	...

TABLE III
SERUM PHOSPHORUS AND CALCIUM VALUES

Date	Phosphorus (mg./100 ml.)	Calcium (mg./100 ml.)
Preoperative		
7/14/58	1.5	11.2
7/15/58	1.7	11.0
9/ 3/58	6.9*	10.0
10/24/58	1.9	11.4
Postoperative		
11/25/58	3.7	9.7
2/24/59	3.9	9.0

* Blood urea nitrogen 27 mg./100 ml. (see Table I).



FIG. 1. The distended, fluid-filled lower ileum at the time of laparotomy. The bowel wall was extremely thin and large quantities of clear, watery fluid could be seen in the lumen.



FIG. 2. The external and cut surfaces of the tumor. The rim of pancreatic tissue which formed the base of the specimen is shown at the top of the photograph.

hours she was still disoriented, and the sensorium became increasingly obtunded. A uremic breath was noted. The blood pressure was 160/70 mm. Hg. The output of urine was small. A specimen of bladder urine showed heavy proteinuria, a sediment containing erythrocytes predominantly, a pH of 5 and a specific gravity of 1.011. The serum bicarbonate was 3 mEq./L., and the potassium had fallen to 2.6 mEq./L. Sodium lactate and additional potassium were administered and hyperpnea followed. She improved rapidly over the next forty-eight hours, during which time the blood urea rose despite a rapidly increasing urinary output. A period of diuresis followed which lasted several weeks.

The patient continued to complain of dysphagia and substernal burning and to regurgitate small amounts of blood-tinged mucus. Roentgenographic examination revealed gastroesophageal reflux but no evidence of peptic ulcer. After the ninth day of hospitalization these symptoms disappeared, and the stools became negative for blood. A repeated roentgenographic examination revealed no gastroesophageal abnormality, but the examination of the small intestine showed dilatation of the distal ileum, with no other findings suggesting disease of the small bowel. A duodenal mucosal biopsy specimen was obtained by means of a Shiner peroral suction biopsy tube, and no significant pathological alterations were found.

The diarrhea improved strikingly, in fact on the sixth and seventh hospital days she was obstipated. However, after the administration of steriods was discontinued on the eleventh hospital day the diarrhea recurred. During a trial without the administration of supplementary sodium the serum sodium concentration fell from 129 to 120 mEq. per L. in the six-day period from September 12 to 18 (Table I), and she lost 3.5 kg. in weight. She was discharged on a regimen of 90 mEq. of potassium and 96 mEq. of sodium bicarbonate daily.

Because of the very striking watery diarrhea in the absence of evidence of significant disease of the small intestine, pancreatic exocrine insufficiency or a primary systemic disorder, a pancreatic islet adenoma was suspected as the cause of the diarrhea. Exploratory laparotomy was recommended after recovery from the acute renal tubular injury.

The diarrhea and nocturia continued, and vomiting recurred. The patient was hospitalized on October 13 and again on October 22 for rehydration. Physical examination disclosed no additional findings except for a non-tender mass in the epigastrium which was felt by one observer. For the first few days she was given intravenous fluids and allowed nothing orally. During examination by proctoscopy at this time the rectum was noted to contain large quantities of cloudy yellow fluid having much the appearance of urine. This fluid was alkaline, and its specific gravity was 1.011. Appropriate investigations failed to demonstrate a communication between the urinary tract and the bowel; the urea content of the rectal fluid was 15 mg. per 100 ml. and nil on two examinations, precluding the presence of significant amounts of urine in the rectal contents.

Laboratory studies revealed no new abnormalities (Tables I and III); the fasting blood sugar was 106 mg. per 100 ml. and the serum total proteins 7.6 gm. per 100 ml., albumin 4.4. gm. and globulin 3.2 gm. In preparation for surgery, the administration of cortisone was begun, 100 mg. intramuscularly daily. On October 25, 1958, laparotomy was performed.

An upper midline incision was made. Exploration revealed the lower esophagus, stomach and duodenum to be normal, without evidence of ulceration. The liver, spleen and gallbladder revealed no abnormalities. No abnormal lymph nodes were seen. The upper small intestine appeared normal, but the ileum and cecum were distended and had extremely thin walls, through which could be seen large amounts of watery fluid in the lumen. (Fig. 1.) The ascending and right

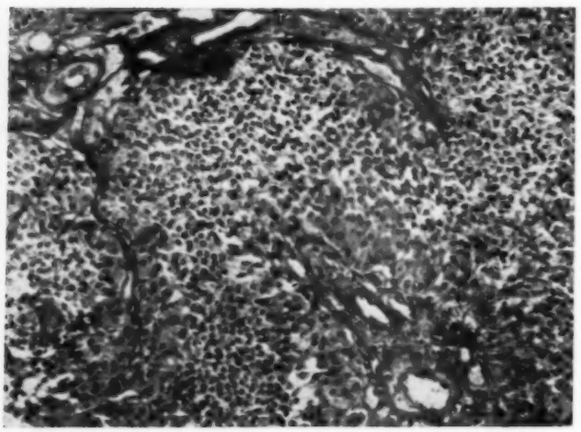


FIG. 3. A cellular area of the tumor showing the cells to be larger in the perivascular zones. Gomori's aldehyde fuchsin stain with Masson trichrome counter-stain. Original magnification × 100.

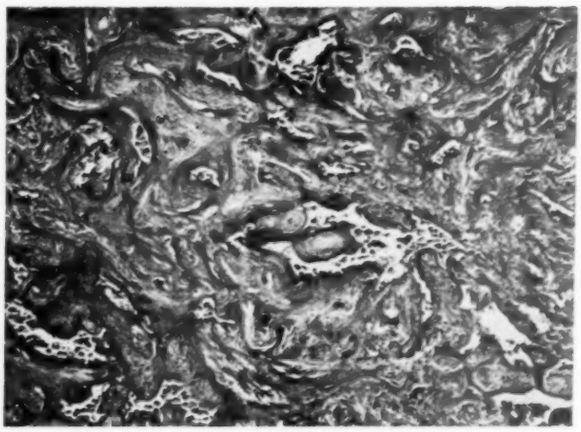


FIG. 4. A section of the tumor showing extensive hyalinization and relative acellularity. Gomori's aldehyde fuchsin stain with Masson trichrome counterstain. Original magnification × 100.

transverse colon were similarly affected, while the left colon and sigmoid appeared normal. In the superior aspect of the mid-portion of the body of the pancreas was a firm, reddish, lobulated tumor (Fig. 2) measuring 5 by 7 cm. and lying in apposition to but not adherent to the celiac axis. The tumor was excised with a surrounding rim of pancreatic tissue. It seemed to be entirely encapsulated. The pancreatic incision was closed with interrupted cotton sutures. The abdominal wound was closed around a drain which led to the vicinity of the pancreatic suture line.

The patient did well postoperatively. Gastric suction was discontinued after four days. Drainage from the wound was slight at first but increased gradually. On the sixth postoperative day suction was applied to the drainage tract. Approximately 250 ml. of clear fluid was obtained daily. On the tenth postoperative day administration of Pathilon® was begun, 20 mg. intramuscularly every six hours. By the twelfth postoperative day all drainage had ceased, and the wound remained dry. The patient had several mucoid stools postoperatively and, on the eighth day, an entirely normal, formed stool. She was discharged on the fifteenth postoperative day, at which time her blood chemistry values were normal except for slight hypokalemia.

Subsequently she did well, with no return of drainage from the wound. The only medications prescribed were multiple vitamins and, at the patient's request, a bulk laxative. Four months after the operation there had been no recurrence of diarrhea or vomiting, and she was having one apparently normal bowel movement daily and nocturia only once or twice a week. Examination revealed no abnormalities. She weighed 53.5 kg. The urine contained, per high-power field, 8 to 10 pus cells and an occasional epithelioid cell. All blood chemical values were normal. (Tables I and III.)

She was last heard from June 16, 1959, eight months after her operation. She was asymptomatic and felt entirely well, and was having one formed stool daily. The nocturia had ceased. She weighed 59 kg.

The description of the surgical specimen is as follows: it consisted of a roughly pear-shaped, brownish red mass which measured 7 by 5.5 by 4 cm. and weighed 120 gm. (Fig. 2.) Except for a narrow rim of pancreatic tissue at the base, it was composed of a tumor with a smooth surface, completely surrounded over the free surface by a thin layer of fibrous tissue in which were many dilated vascular channels. The sectioned specimen revealed gross lobulation of that portion of the tumor adjacent to the attached pancreatic tissue. The substance of the tumor bulged outward from the cut surface. It had a mottled tan color and it was uniformly soft except in one area about 1 cm. in diameter which was extremely firm, yellow and partially calcified. Multiple 1 mm. cystic areas were noted throughout the tumor.

Microscopic examination revealed that surrounding the free surface of the tumor there was a thin band of fibrous tissue which became deficient and interrupted where the tumor apposed pancreatic tissue. Small, non-encapsulated nodules of tumor tissue, separate from the main mass, extended to the margin of the specimen. The tumor consisted of varying concentrations of small cells and loose stroma. In some areas the tumor was composed almost entirely of cells, while in other large areas the cells were virtually replaced by hyaline, acellular fibrous tissue. (Figs. 3 and 4.) Many large, thin-walled, sinusoidal blood vessels and small, thick-walled blood vessels coursed through the specimen. In most places sheets and columns of cells were separated by a loose fibrous stroma showing many areas of hyalinization. The cystic spaces noted in the gross description were found to be areas of liquefactive degeneration.

The cells of the tumor were approximately the shape and size of normal cells of the islets of Langerhans, and

they exhibited a similar degree of variability in nuclear size. The cells of the perivascular areas were relatively larger than those elsewhere. The cytoplasm of the cells was finely granular, and the nucleoli were more numerous and slightly larger than their normal islet cell counterparts. Mitotic figures were rarely seen. No definite evidence of vascular or lymphatic invasion could be demonstrated. No ductal or acinar cells were found within the tumor. Detailed cytochemical studies of the tumor are in progress, and the results will be published separately [*4*]. These studies seem to exclude the normally reacting alpha or beta cell as the cell of origin of the tumor.

The final pathological diagnosis was islet adenoma of the pancreas with characteristics suspicious of malignancy. Portions of the surgical specimen were also examined by Dr. Ashton B. Morrison of the Department of Pathology of the University of Pennsylvania School of Medicine, Philadelphia. He observed that the tumor was similar in its characteristics to the others which he has seen in association with this type of history [*5*].

COMMENTS

The striking features of this patient's illness were the persistent watery diarrhea, the recurring episodes of nausea and vomiting, the severe potassium depletion and the paucity of evidence on physical or laboratory examination of pancreatic or intestinal disease. It is noteworthy that the diarrhea improved strikingly on two occasions during adrenal steroid therapy, as was the case also with the patient reported by Priest and Alexander [*1*].

Of interest in this patient was the extreme thinning of the wall of the ileum and cecum seen at laparotomy and the presence of a remarkable amount of watery fluid within the lumen of the ileum and large bowel. The profuse serous fluid which was repeatedly observed in the rectum also was striking. It seems clear that the absorptive function of the ileum and cecum was insufficient in this patient, leading to the loss of large quantities of fluid. It is a matter of speculation whether this failure of fluid absorption was secondary to an excessive influx of pancreatic or gastrointestinal secretion, exceeding the absorptive capacity of the ileum and cecum, or to inhibition of absorption, perhaps by a humoral substance elaborated by the tumor. We favor the possibility of inhibition of function of the ileum and cecum, and believe that the atrophic appearance of the bowel at laparotomy supports this hypothesis.

Hypophosphatemia has been a feature of a number of the reported cases. Among the possible explanations for this finding is the likelihood of a sizable loss of phosphate, as well as of calcium, into the intraluminal fluid of the ileum and cecum.

Lastly, it should be noted that there was no convincing evidence of peptic ulcer in this patient, clinically or at laparotomy. The source of the upper gastrointestinal hemorrhage during the July 1958, exacerbation was not ascertained. It seems likely that it was a manifestation of a lesion which was secondary to the repeated vomiting.

SUMMARY

A patient is reported on who presented the syndrome of persistent, incapacitating watery diarrhea, severe dehydration and potassium depletion associated with a pancreatic islet adenoma. Removal of the tumor was followed by complete remission of symptoms.

Acknowledgment: We are indebted to Dr. Ashton Morrison for reviewing portions of the surgical specimen and for comparing the findings with those of similar cases which he has had the opportunity to review.

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Primary Myoglobinuria (Meyer-Betz Disease)*

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Primary myoglobinuria, a rare disease of unknown etiology, was first described in 1910 by Meyer-Betz [*1*]. Despite its usual striking symptomatology, until the present report only thirty-six cases have appeared in the literature.

Myoglobin may appear in the urine in any situation in which there is dissolution of the muscle sarcoplasm. The intracellular components of the destroyed fibers enter the circulatory system and myoglobin, at least, is excreted by the kidney. Thus there are several conditions distinct from primary myoglobinuria in which myoglobin makes its appearance in the urine. These have been succinctly classified by Whisnant et al. [*2*] and are generally referred to as the secondary myoglobinurias. Included are the crush syndrome, high-voltage shock, arterial occlusion with ischemia, and Haff disease.

It is easily understandable that myoglobin may be excreted in the urine in crush injuries, arterial occlusion and electric shock. The mechanism in Haff disease [*3*], however, deserves comment. Often termed epidemic myoglobinuria, this disease is undoubtedly the most common cause of the appearance of the pigment in the urine. It occurs in East Prussia, Sweden, and in Northwestern Russia [*3,4*]. Those afflicted persons manifest muscular pain and stiffness, and the passage of dark urine. Attacks are multiple and seem to bear some relation to the ingestion of fish and eels. The poisoning of the fish and eels by the waste products from nearby cellulose factories is believed to be the underlying etiological factor.

In sharp contrast to these conditions, primary myoglobinuria is characterized by acute episodes of muscular pain and dysfunction in association with the passage of mahogany colored urine, with muscular exertion as the usual sole precipitating factor.

The literature repeatedly points out the fact that diagnosis is difficult because of the problems involved in identification of the pigment myoglobin. This statement is in part true, for identification of the protein pigment is indeed not without difficulty. However, successful diagnosis can be relatively easy when awareness is combined with certain basic and simple laboratory procedures.

The patient presented herein strikingly demonstrates the classic clinical and laboratory findings in this disease.

CASE REPORT

A twenty-three year old married white male student was admitted because of painful muscles and the passage of dark urine. He had always been in good health and was active in athletic activities. As a high school student he had played varsity football and baseball, and for the past eight years had been a member of school wrestling teams.

Two days prior to admission he took a physical condition test during which he performed nine pull-ups, seventy sit-ups, eighty squat-jumps, fifty push-ups, and ran a timed 300 yards. Within an hour following this activity he noted severe soreness of the muscles of his thighs. Later that evening he noted increasing pain as well as extreme tenderness and stiffness of his legs. He was unable to sleep that night because of his severe discomfort. On the following day his soreness and stiffness persisted and his legs seemed very weak. The second evening he was again unable to sleep. The pain was so great that he could hardly move his legs and he noted that his quadriceps muscles felt extremely hard. He arose and on passing his urine was surprised to note that it was dark brown in color. When he walked his legs seemed to give way and he would stagger, barely saving himself from falling on several occasions. He noted no chills, nausea, vomiting or abdominal pain. There was no excessive soreness of other muscle groups and, although he felt poorly, he did not believe himself to be febrile.

Physical examination revealed a well developed and well nourished, muscular, white man complaining of severe pain in his upper legs. His temperature was 99.6°F. orally, pulse 90 per minute, respirations 18 per minute, and blood pressure 132/80 mm. Hg. There was no pallor nor was there scleral icterus. The lungs were clear to auscultation and percussion. Examination of the heart revealed no abnormalities. Palpation of the abdomen disclosed no abnormal masses.

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Examination of the legs revealed that the patient was unable to flex the knees beyond twenty degrees. The quadriceps muscles were exquisitely tender to pressure and so hard as to be board-like. The knee jerks were absent and the ankle jerks depressed. The remainder of the examination was within normal limits.

Laboratory examination revealed the hematocrit to be 50 per cent, hemoglobin 16 gm. per cent, white blood count 11,700 per cu. mm. with 85 per cent neutrophils, and the reticulocyte count 0.6 per cent. The total bilirubin was 1.3 mg. per cent with 0.9 mg. per cent in the indirect fraction, serum potassium 6.5 mEq. per L., non-protein nitrogen 32 mg. per cent, total protein 6.6 gm. per cent, and serum creatinine 1.75 mg. per cent. Results of the Coombs test and serological tests for syphilis were negative. Osmotic fragility and four-hour glucose tolerance test were within normal limits. The patient's serum was colorless. However, despite this, it gave a strong positive reaction when tested with benzidine or guaiac.

The urine was a dark brown color. It had a pH of 6, a specific gravity of 1.021, no sugar and 4-plus albumin. The sediment contained only amorphous granules without casts, or red or white cells being present. Results of tests for urine bile and urobilinogen were negative; however, the specimen gave a strong positive reaction when tested with benzidine or guaiac. Examination for porphyrins revealed no abnormalities. The total urinary protein was 4.32 gm. per L. The urine creatine was 89 mg. per 24 hours (normal zero to 50 mg. per twenty-four hours) and the creatinine 1.32 gm. per twenty-four hours. Results of an ammonium sulfate saturation test for the presence of myoglobin in the urine were positive. Electrophoretic study of the urine revealed the presence of myoglobin. (Fig. 1.) Roentgenograms of the chest and abdomen were normal as was the electrocardiogram.

The patient was placed at complete bed rest. He continued to pass dark urine and to complain of pain and stiffness of his legs. After his first hospital day he became afebrile. Gradually the muscles of his thighs began to soften, his pain decreased, and his urine began to lighten. Urinary output was well maintained. By the tenth hospital day he was free of symptoms except for minimal weakness, his urine was of normal color and free of protein. During the patient's course serial benzidine and guaiac tests made on his urine and colorless serum became negative.

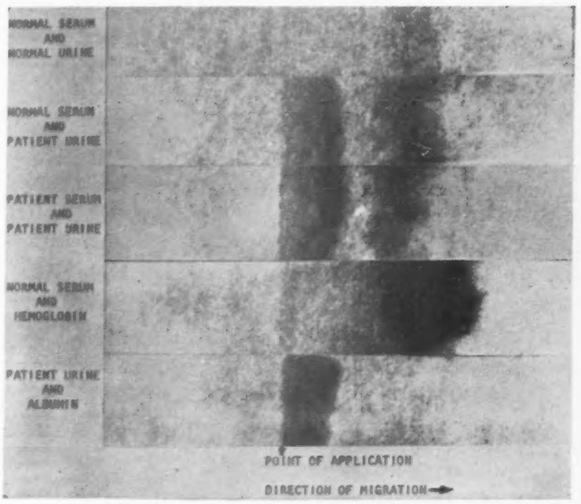


FIG. 1. Electrophoretic pattern. Note the heavy band of myoglobin present in the patient's urine, easily distinguished as it migrates less than half the distance of the hemoglobin. Human serum contains a small amount of hemoglobin, thus accounting for the presence of that band in some of the mixtures; only the myoglobin band is present when the patient's urine is mixed with albumin.

COMMENTS

Numerous observers, attracted by the interesting and often dramatic picture presented by their patients, have advanced their ideas concerning the nature of primary myoglobinuria. Certain facts are known, but several facets of the disease afford opportunity for speculation.

Myoglobin is a respiratory pigment found in the sarcoplasm of muscle. It was first established as an independent component of muscle in 1871 when it was found in the thoracic musculature of the mollusca, which lack blood hemoglobin [*5*]. Mörner [*6*] established its spectroscopic identity in 1897 and, in 1933 Theorell [*7*] prepared it in crystalline form, thus establishing its unique identity beyond further question. Myoglobin differs from hemoglobin in that its protein moiety is considerably smaller, the molecular weight being 17,500 while that of hemoglobin is 68,000. The smaller molecular size accounts for its low renal threshold, estimated at 15 mg. per 100 cc. of blood in contrast to that of 100 to 150 mg. per 100 cc. for hemoglobin [*8*]; with its relatively low molecular weight, myoglobin is rapidly filtered by the glomerulus and hence quickly cleared from the plasma. Thus we may explain the colorless plasma in attacks of myoglobinuria, since the concentration of plasma does not reach high enough levels to impart a red color. The solubility and diffusibility of myoglobin is considerably greater than that of hemoglobin and it has a greater affinity for oxygen. The absorption spectrums of the two pigments are quite similar, myoglobin exhibiting an alpha-band peak at 581 to 582 and a beta-band peak at 542 millimicrons. Hemoglobin exhibits an alpha-band peak at 578 and a beta-band peak at 540 millimicrons.

The typical attack of primary myoglobinuria

TABLE 1
DIAGNOSTIC OUTLINE FOR PRIMARY MYOGLOBINURIA

- Clinical data
  - Preceding history of muscular exertion
  - Inordinate muscular pain, stiffness and tenderness
  - Passage of dark red-brown urine
- Laboratory data
  - Basic procedures
    - Urine that gives a positive reaction with benzidine reagent in the absence of significant numbers of red cells
    - Normal-colored blood plasma that gives a positive reaction to benzidine reagent
    - Absence of evidence of hemolysis
    - Ammonium sulfate saturation test positive for myoglobin
  - Specialized procedures
    - Paper electrophoretic analysis
    - Spectroscopic analysis
    - Ultracentrifugation
    - Abnormal muscle biopsy

is heralded by severe muscle pain and general malaise. Within a few hours the pain increases and the muscles become stiff, hard and swollen. The patient is astonished to find that his urine is a dark brown mahogany color. Most frequently, as in the patient herein described, the lower extremities are involved, but at times the upper extremities and trunk may be affected. The deep tendon reflexes may be temporarily diminished or absent and the involvement of the muscles may be so severe as to cause temporary paralysis. As a result of renal cortical irritation, oliguria and anuria may supervene with production of the syndrome of acute renal failure.

In this patient the attack was preceded by muscular exertion. This is true in about half of the patients reported on. It is of interest that to date the exertional form has been reported only in males. In some cases the episodes have been spontaneous [*9,10*] and others have followed a variety of conditions such as upper respiratory infection [*9*], fever [*11*] and electroshock therapy [*12*].

Muscle power returns slowly. Apparent complete recovery may occur in one to three weeks or there may be residual weakness. Six patients are known to have had permanent muscle atrophy, some of them severe enough to resemble progressive muscular dystrophy [*13,14*]. After recovery from an acute attack the patient appears healthy, but the likelihood of further attacks is great.

Laboratory examination reveals the dark red-brown urine to give a strongly positive reaction with benzidine reagent. There is heavy proteinuria but red cells are absent unless there has been renal irritation. There is no anemia and the patient's blood plasma, of normal color, gives a positive reaction with benzidine reagent because of the presence of myoglobin. Serum bilirubin, the Coombs test, red cell fragility, urine urobilinogen and urine bile reveal no abnormalities. Examination for porphyrins reveals none. The reticulocyte count is normal, but there may be a mild leukocytosis. The creatine and creatinine pattern may be abnormal. The values in the patient reported on are in keeping with the findings of Kreutzer et al. [*13*] and Bowden et al. [*9*] who described high creatine and normal or low excretion of creatinine during acute attacks. The ammonium sulfate saturation test, as described by Blondheim, Margoliash and Shafir [*15,*] bears out the presence of myoglobin. Ultracentrifugation, spectroscopic analysis or paper electrophoretic study of the urine may be employed for confirmation. Recently, Whisnant et al. [*10*] described an electrophoretic method using special staining technics by which definite identification of the pigment can be made. Use was made of the procedure for definitive identification of myoglobin in the urine of this patient.

The etiology of primary myoglobinuria is unknown. The disease usually has its earliest manifestations in childhood or adolescence [*9*] but the first attack may not occur until well into adulthood. Some observers favor a predisposing familial or hereditary factor [*13,16,17,18,19*] with muscular exertion acting as a trigger mechanism. Whisnant et al. [*10*] state the hypothesis that primary myoglobinuria may represent a genetic defect in the enzyme system of the muscle cell, which becomes symptomatic with varying factors in the environment. The fact that the disease has been described as attacking multiple members of a family is relevant [*9,19*].

All observers agree that there is dissolution of muscle sarcoplasm with liberation of muscle cell contents. It is reasonable to suppose that one of two factors must be operative [*22*]. Either the muscle fibers themselves are defective or the environment surrounding the fibers is unfavorable. What part heredity, predisposing familial factors or trigger mechanisms play, however, remains conjectural.

Pathologically there are widespread changes in striated muscle [*9,20,21*] with segmental necrosis, loss of striations, clumping of myofibrils, vacuolization, and formation of granular protein precipitate in the sarcolemmal tubes.

Proliferation of sarcolemmal nuclei and the presence of multinucleated giant muscle cells may be seen, suggesting areas of regeneration. However, considerable variation has been reported. This probably relates to the stage of the disease at which the particular studies were made.

Diagnosis, despite the inherent difficulties in identification of myoglobin, can be successfully achieved through a combination of awareness of certain clinical features and a few relatively simple laboratory procedures. (Table I.) It depends essentially upon differentiation from various hemoglobinurias and from the porphyrias. Since myoglobin is a heme pigment it imparts a positive benzidine test to urine, but does not fluoresce under ultraviolet illumination. Porphyrins, in contrast, show strong fluorescence, but do not produce a positive benzidine reaction. The hemoglobinurias invariably impart a red color to the blood plasma as they elevate the plasma hemoglobin. As mentioned previously because of the low renal threshold of the pigment and hence the rapid clearing, the plasma of the myoglobinuria patient is colorless. With such evidence a presumptive diagnosis of myoglobinuria is secure. An ammonium sulfate saturation test [*15*] can then be employed for confirmation. Final identification of the pigment may be achieved by electrophoretic analysis [*10*]. It is to be emphasized that such identification, though desirable, is not essential to diagnosis.

The prognosis in this disease is relatively good. However, it is to be noted that the illness is not wholly benign, eight fatal cases having been reported [*9*]. If there is sufficient renal cortical irritation, acute renal failure can ensue. Gillett [*23*] called attention to this fact and stressed the danger of inducing attacks.

There is no known specific treatment or prophylaxis for the disease, save avoidance of undue exertion when it appears to be the precipitating factor. During the acute attack bed rest is essential and careful observation of renal function mandatory.

SUMMARY

A case of acute idiopathic primary myoglobinuria occurring in a young adult man is presented. The patient strikingly demonstrates the clinical manifestations and laboratory findings in this apparently rare illness. The ammonium sulfate saturation test was employed for diagnostic confirmation, and electrophoretic analysis unequivocally demonstrated the presence of myoglobin.

The clinical, laboratory and pathological findings in the disease are described, and theories of pathogenesis reviewed.

Acknowledgment: I am indebted to Capt. James P. Hooper, MSC, Chief, Biochemistry Section, Fifth Army Laboratory, St. Louis, Missouri, for his assistance in performing the electrophoretic analysis.

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Nephrogenic Diabetes Insipidus Caused by Amyloid Disease*

Evidence in Man of the Role of the Collecting Ducts in Concentrating Urine

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CONSIDERABLE evidence in experimental animals indicates that urine is concentrated in medullary collecting tubules by the diffusion of water back through the wall of the collecting duct into interstitial fluid rendered hyperosmotic by a counter-current multiplier system involving the loops of Henle and the vasa recta [*1*].

The present report deals with an unusual case of renal amyloidosis. The patient, despite relatively mild depression of other renal functions, was unable to concentrate urine above the osmolality of plasma. Microdissection of the kidneys revealed deposits of amyloid localized primarily to the basement membrane of the medullary collecting ducts without involvement of the loops of Henle. It is postulated that interference with the diffusion of water out of the collecting ducts accounted in part for the impairment in concentrating ability which was observed.

CASE REPORT

V. M. (G.N.H.H. No. 47-77-41) was a thirty-seven year old white man with a history of osteomyelitis between fourteen and twenty-two years of age resulting in immobilization of the left knee joint. He had experienced polydipsia, polyuria and nocturia for several years. Three months prior to death, while recovering from pneumococcal pneumonia, he was found to have a carcinoma of the lung.

While under observation, the daily urinary output varied from 3 to 6 L. Random urinary specific gravities ranged from 1.002 to 1.012. Albuminuria was always present and a twenty–four-hour collection of urine contained 1.5 gm. of protein. The urinary sediment revealed no abnormalities. One urine culture grew out Escherichia coli; this bacteriuria, which was asymptomatic, was treated with Achromycin.® An intravenous pyelogram showed poor visualization of the upper urinary tract with normal appearing calyces and ureters, and normal renal outlines. The blood pressure was 140/80 mm. Hg. The blood non-protein nitrogen was 33 mg. per cent, the phenolsulfonphthalein excretion was 15 per cent in fifteen minutes and 40 per cent in two hours. The serum sodium, potassium, carbon dioxide and chlorine were all normal. Serum calcium and phosphorus were 9.8 and 4.5 mg. per cent, respectively. Several determinations of serum alkaline phosphatase were normal. Serum albumin was 3.1 gm. per cent and serum globulin was 3.8 gm. per cent, with slight increases in alpha$_2$, beta and gamma fractions by electrophoresis. Bence Jones protein was found in the urine once, but not on several subsequent occasions.

The excretion of large volumes of dilute urine suggested the diagnosis of diabetes insipidus, possibly secondary to carcinomatous metastasis to the hypophysis. Accordingly, a Hickey-Hare test was performed, the results of which are diagrammed in Figure 1. It should be emphasized that at the time the test was carried out the patient felt well, had been eating normally and exhibited no signs of wasting, and had no chemical or clinical evidence of hypercalcemia or potassium depletion.

After fourteen hours of water deprivation the urinary osmolality was 201 mOsm. per kg. at the same time that the plasma osmolarity was 290 mOsm. per kg. Infusion of 300 ml. of 3 per cent sodium chloride did not result in increased urinary concentration, although the flow of urine declined somewhat, from 10 ml. per minute to 6 ml. per minute. Unlike the expected sequence of events in a patient with true

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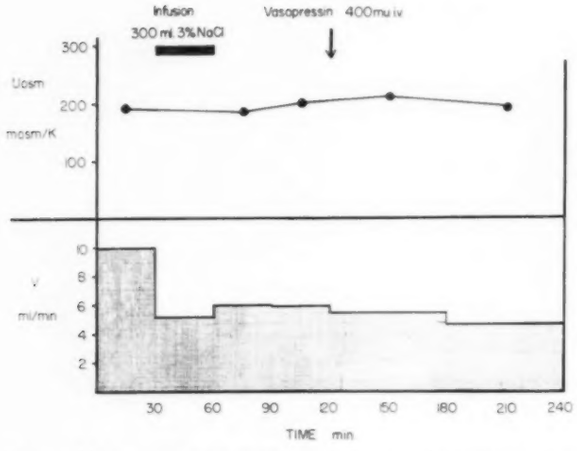


FIG. 1. Urine was dilute and remained so throughout the Hickey-Hare test. Infusion of hypertonic saline solution or of vasopressin did not produce a significant rise in urinary osmolality.

diabetes insipidus, the urine remained dilute despite the injection of 400 milliunits of vasopressin intravenously. On two subsequent occasions the kidneys were again shown to be unresponsive to the administration of exogenous vasopressin, excreting a urine of only 298 and 301 mOsm. per kg. both before and after the subcutaneous injection of 10 units of aqueous vasopressin or the intramuscular administration of 5 units of vasopressin in oil. Other samples of the same lot of vasopressin were repeatedly shown to be effective in interrupting water diuresis and producing maximal urinary concentration in normal persons.

Three months after these tests the patient was admitted to the hospital because of transient shortness of breath and pleuritic chest pain. He died suddenly of a massive pulmonary embolus.

Postmortem observations were as follows: the kidneys were fixed in formalin and Zenker's solution. Histological staining, in addition to hematoxylin and eosin, included the periodic acid-Schiff, Lugol's iodine and crystal violet stains for amyloid, and flaming red for fat. The technic of microdissection was that of Oliver [2]. All dissected tubules were studied by phase contrast microscopy and in some instances they were stained with iron hematoxylin, Lugol's iodine, methyl violet or flaming red. Continuous comparisons were made between the characteristics of lesions in histological and microdissected material. Notes and drawings were made of dissected specimens and photomicrographs were taken of typical structural changes. These were taken with phase contrast microscopy using unstained specimens. Phase contrast produces a bright halo effect which outlines the tubular segments and a dark background in contact prints. For this reason the background was cut away with a razor blade before the prints were mounted.

Postmortem examination revealed an epidermoid carcinoma of the right lung with metastasis to lymph glands, bone and adrenal glands, bilateral femoral vein thrombosis with embolism of major pulmonary arteries, and amyloid deposition in the liver and spleen. There were no metastases to the pituitary gland or hypothalamus.

The right and left kidneys weighed 135 and 310 gm., respectively. The capsule of the right kidney stripped with moderate difficulty and its surface was irregular due to coarse scarring. The cortex was slightly reduced in thickness, yellow-tan in color and not well demarcated from the medulla. The medulla, calyces and pelvis appeared normal. The left kidney, except for its large size due to compensatory hypertrophy, revealed no abnormalities at gross examination. Microscopic examination of the kidneys revealed two types of pathological change, namely, amyloid deposi-

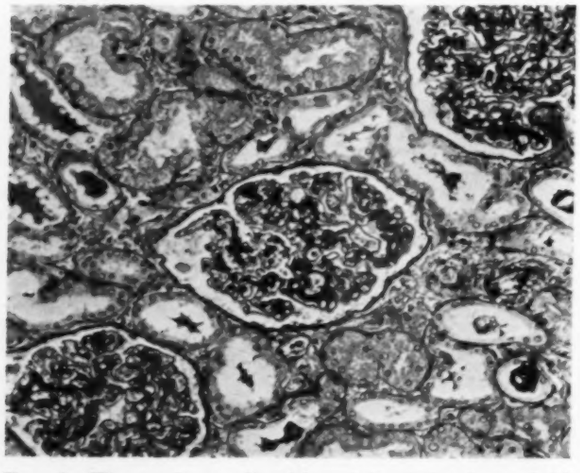


FIG. 2. Three glomeruli with minimal focal amyloid change in a few vascular loops. Amyloid is absent in the tubules. The three tubular segments show hydropic swelling. Periodic acid-Schiff stain × 150.

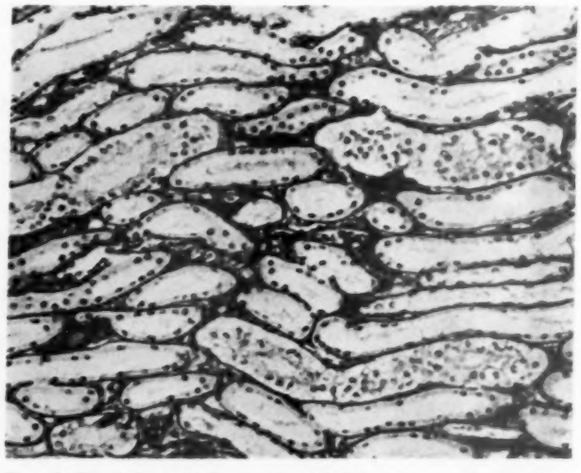


FIG. 3. Straight tubules in a medullary ray at the corticomedullary junction; no amyloid deposition. Hematoxylin and eosin × 150.

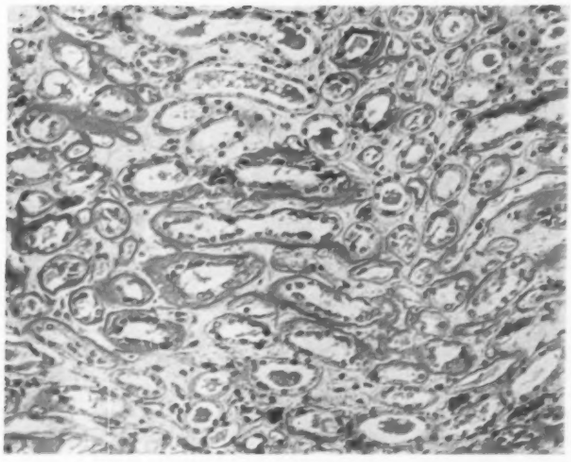


FIG. 4. Tubules in the outer medulla. Amyloid of patchy distribution is present within a few collecting ducts. Hematoxylin and eosin × 150.

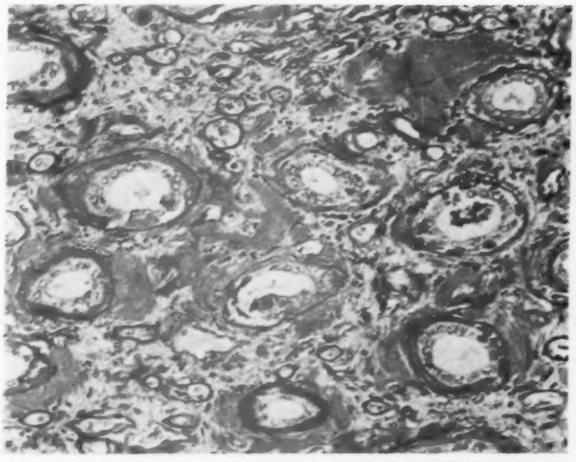


FIG. 5. Extensive amyloid deposition in large collecting ducts of the inner medulla. The amyloid is chiefly within the tubular basement membranes between the latter and the epithelial cells. In several places the basement membranes are deficient, with extension of amyloid material into the interstitial space. Periodic acid-Schiff stain × 150.

tion and chronic pyelonephritis, the latter being confined to the right kidney.

Chronic pyelonephritis of the right kidney was apparent as irregular regions of interstitial fibrosis with lymphocytes in the medulla and cortex which caused U-shaped depressions of the cortical surface. In the cortex, several glomeruli were trapped in the regions of fibrosis and these were in various stages of sclerosis with pericapsular fibrosis. The tubules showed both atrophy and dilatation and some contained hyaline casts. Evidence of an acute inflammatory process was not seen.

The distribution of amyloid was about the same in the two kidneys, being found in the following sites: interlobular arteries, afferent arterioles and vasa recta, glomeruli, collecting tubules, and intertubular stroma of the medulla. There was no amyloid in renal vessels larger than interlobular arteries. Minimal amyloid distribution was seen in an occasional interlobular artery and this involved only small areas of the vessel wall. Many afferent arterioles showed prominent amyloid change, frequently resulting in some narrowing of the vessel lumina. Approximately one in four glomeruli contained minimal amyloid deposits which involved only a few vascular loops. (Fig. 2.)

There was no amyloid in tubules located in the cortex (Figs. 2, 3 and 7) except for slight deposition in a rare tubule in a medullary ray. The most striking amyloid deposition occurred in medullary collecting tubules. (Figs. 4 through 7.) Amyloid was also present to a lesser degree in the vasa recta of the medulla. Amyloid change in the collecting ducts was most marked in the inner medulla (Fig. 5) and it gradually diminished in the outer medulla (Fig. 4) so that only a rare cortical collecting tubule contained amyloid material. During microdissection, all medullary collecting ducts were found to contain amyloid if traced far enough into the medulla. (Fig. 7.) At the corticomedullary junction, amyloid in collecting tubules was of irregular patchy distribution (Figs. 4 and 7); however, as the ducts passed through the

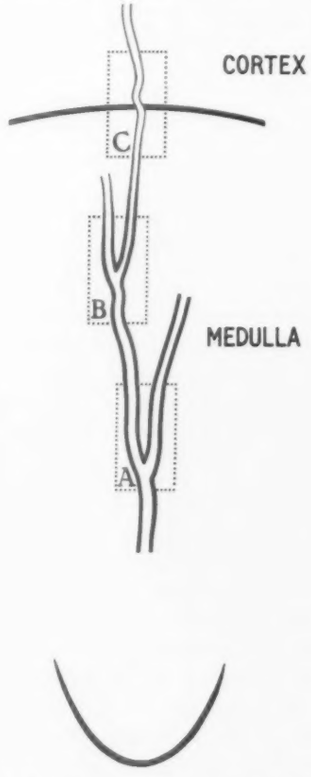


FIG. 6. Artist's drawing showing the relative positions of microdissected segments A, B and C in Figure 7 from a continuous collecting duct arborization. Amyloid deposition is shown as a thickening of the basement membrane.



FIG. 7. Segments of a continuous collecting duct arborization shown diagrammatically in Figure 6. The basement membranes of segments A and B from the medulla are markedly thickened by amyloid. In several places (arrows) there is separation of the amyloid and the tubular epithelium. Cellular detail is not clear because of the great amount of amyloid within the tubules. In segment C, from the corticomedullary junction, there is minimal patchy amyloid deposition below, but the remainder of the tubule reveals no abnormalities, with a thin basement membrane and normal cellular morphology. Original magnification × 100.

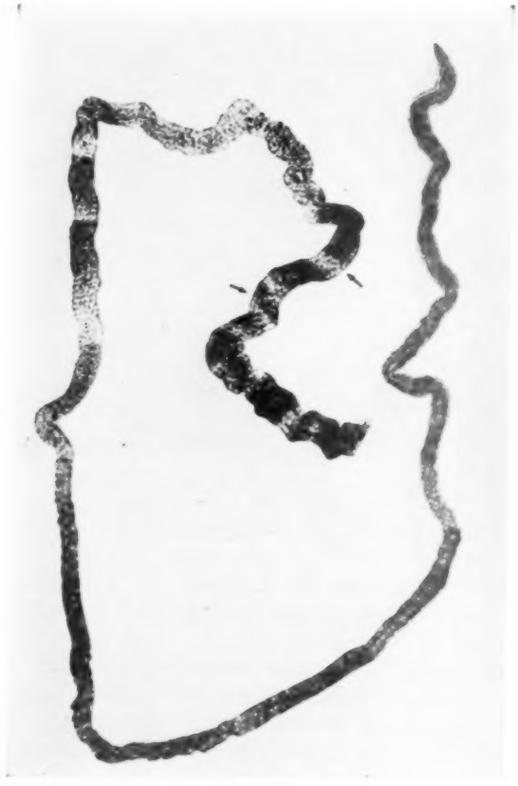


FIG. 8. Terminal segment of a proximal convolution, thin and ascending limbs of Henle's loop. The epithelial cells of the proximal convolution show hydropic swelling (arrows). The tubule otherwise reveals no abnormalities and there is no amyloid deposition. Original magnification × 100.

medulla to the papillary tip the deposition became uniform and increased in amount (Figs. 5 and 7) so that the large collecting ducts in the inner medulla contained the greatest amount of amyloid. This material stained for amyloid with Lugol's iodine and crystal violet in histological preparations, but there was weak staining with Lugol's iodine and no staining with crystal violet in microdissected specimens. This might be explained by chemical alteration of the amyloid resulting from maceration in concentrated hydrochloric acid prior to microdissection. Amyloid stained weakly positive with periodic acid-Schiff reagent. In the collecting tubules, amyloid was deposited on the inner surface of the intensely PAS-positive basement membranes (Figs. 4 and 5), i.e., between the basement membranes and the epithelial cells. Occasionally, in histological material, there were focal deficiencies of the basement membranes where amyloid extended into the intertubular stroma. (Fig. 5.) These appeared in microdissected specimens as irregular masses attached to the tubules; however, no true breaks in the tubular basement membranes were otherwise encountered.

Normally, the basement membranes in microdissected tubules are extremely thin. The basement membranes in collecting tubules with amyloid deposition were enormously thickened, and separations between the basement membranes and epithelium often occurred. (Fig. 7.) These were probably artefactual as a result of maceration and dissection since they were not seen histologically. Epithelial cells in these tubules were not easily visualized because of the greatly thickened basement membranes. (Fig. 7.) Cellular detail, however, revealed no abnormalities except for occasional intracellular droplets which did not stain for fat but were PAS-positive.

Terminal portions of the proximal convolutions showed mild hydropic changes. (Figs. 2 and 8.) The cells were swollen with clear fluid, with little alteration of nuclei or cellular organelles.

Approximately one-third of the medullary vasa recta showed amyloid deposition. This was irregular

and patchy in distribution, and slight in amount when compared to the collecting ducts. Basement membranes of the distal portions of proximal convolutions and loops of Henle (descending and ascending limbs) in the medulla contained no amyloid (Fig. 8) even though they traversed regions of amyloid deposition in the intertubular stroma. Likewise, the proximal and distal convolutions in the cortex were free of amyloid. (Figs. 2 and 3.)

COMMENTS

The marked degree of involvement of the medullary collecting ducts by amyloid in the present case is distinctly unusual. Renal amyloid is generally found chiefly in vascular structures, including the glomeruli. Although Bell [*3*] noted occasional accumulations under the basement membranes of the straight tubules or in the interstices of the medulla, he encountered significant deposition of amyloid in renal tubules in only two of 65 patients and in both of these the cortical tubules rather than those of the medulla were involved. By contrast, deposits of amyloid in the glomeruli, blood vessels and cortical structures were minimal in this patient, in comparison with its extensive deposition in the medullary collecting ducts.

Loss of concentrating ability is a common symptom of advanced renal disease, in which it is often ascribed to the increased load of solutes excreted per nephron, the effect being analogous to the fall in urinary concentration which occurs when solute diuresis is induced in subjects with intact kidneys. Such an explanation does not, however, account for the specific impairment of renal concentrating ability observed in this case. In most diseases of the kidneys, maximum urinary solute concentration does not become fixed at that of plasma until moderate azotemia is established. In the experiments of Hayman et al. [*4*] in dogs, two-thirds of both kidneys were ablated before significant hyposthenuria was produced. In certain other pathological states characterized by morphological changes in the collecting ducts of the kidneys, including potassium depletion [*5,6*] and nephrocalcinosis [*7,8*] renal concentrating capacity appears to be specifically and disproportionately impaired before glomerular filtration is restricted, and prior to the development of azotemia.

The functional and morphological findings in the present case are of particular interest insofar as they bear on current theories of the mechanism by which the kidneys produce a concentrated urine [*1*]. Wirz [*9*] and Gottschalk and Mylle [*10*] have demonstrated that urine entering the distal convoluted tubule of a hydropenic rat is hypotonic to plasma, reaches the concentration of plasma in the distal tubule, and becomes progressively more concentrated as it passes down the collecting ducts. It seems clear that, during hydropenia, the concentration of sodium in renal tissue, including blood and interstitial fluid [*11–13*], also increases progressively from cortex to papillary tip, and generally exceeds that present in peripheral plasma or in bladder urine [*12*]. This gradient of sodium concentration in interstitial fluid is probably created and maintained by active transport of sodium from Henle's loops in conjunction with counter-current flow in both the hairpin loops of Henle and the capillaries looping down into the medulla [*1,10,11*]. (Active reabsorption of sodium from the collecting ducts [*14*] may also play a role in this process.) Antidiuretic hormone is thought to increase the permeability of the collecting ducts to water and thereby permit the initially isotonic urine delivered to the collecting ducts from the distal tubules to become as hypertonic as the interstitial fluid of medulla and papilla.

The remarkable thickening of the lining of the collecting ducts observed in this case might be expected to interfere with the back-diffusion of water from the lumen of the duct and to result in a state resembling diabetes insipidus, which, however, would be unresponsive to antidiuretic hormone. Because the cuffs of amyloid were uniquely localized to the collecting ducts of the medulla, with little involvement of more proximal portions of the nephron, it would be anticipated that the maximum concentration of the urine, achieved after dehydration or injection of vasopressin, would be close to that of plasma (distal tubular fluid). Polyuria and polydipsia would be less marked in such circumstances than in true diabetes insipidus, in which the urine is usually considerably more dilute than plasma. On the other hand, in the present case urine hypotonic to plasma might be produced in the course of a solute diuresis, even in the presence of vasopressin, because of the augmented flow of hypotonic urine delivered to the distal tubule.

In addition to reducing the permeability of the collecting ducts to water, the extensive deposits of amyloid might have interfered with reabsorption of sodium from the collecting ducts and therefore with the maintenance of a high

concentration of sodium in the renal papilla. Amyloid deposition did not, however, involve the loops of Henle, and these, rather than the collecting ducts, are generally considered to play the major role in establishing the normal gradient of sodium concentration in the medullary interstitial fluid [*10*]. Interference with normal counter-current flow through capillary loops supplying the medulla might also, on theoretical grounds, impair concentrating ability, but morphological evidence of the involvement of blood vessels was relatively sparse, minimal deposits of amyloid being present in perhaps one-third of the vasa recta. It is tempting to postulate that the thick cuffs of amyloid surrounding the collecting ducts in the medulla were chiefly responsible for the striking impairment of renal concentrating ability demonstrated during life, by restricting the back-diffusion of water from these tubules.

SUMMARY

A patient with renal amyloidosis was found to have marked impairment of renal concentrating ability, with polyuria and hyposthenuria unresponsive to vasopressin therapy. Postmortem microdissection studies revealed that the deposits of amyloid were localized chiefly in cuffs surrounding the medullary collecting ducts. These findings underline the role of the collecting ducts in the production of a concentrated urine in man.

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1. Andrews, M. C.; Andrews, W. C., and Strauss, A. F.: Effects of Progestin-Induced Pseudopregnancy on Endometriosis: Clinical and Microscopic Studies, Am. J. Obst. & Gynec. *78:776* (Oct.) 1959.
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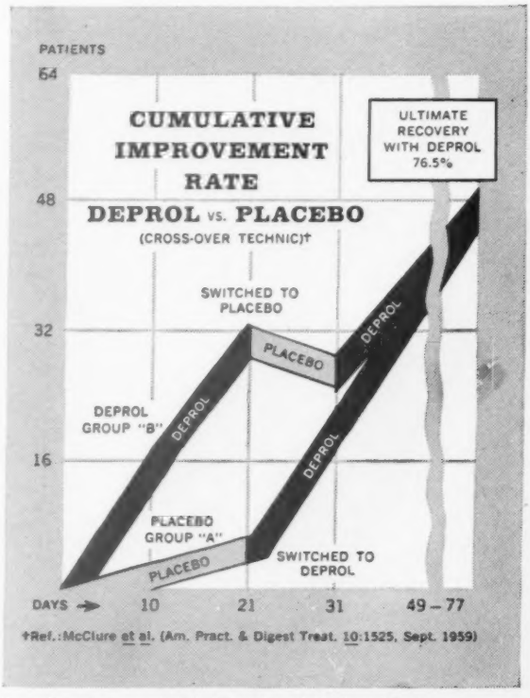
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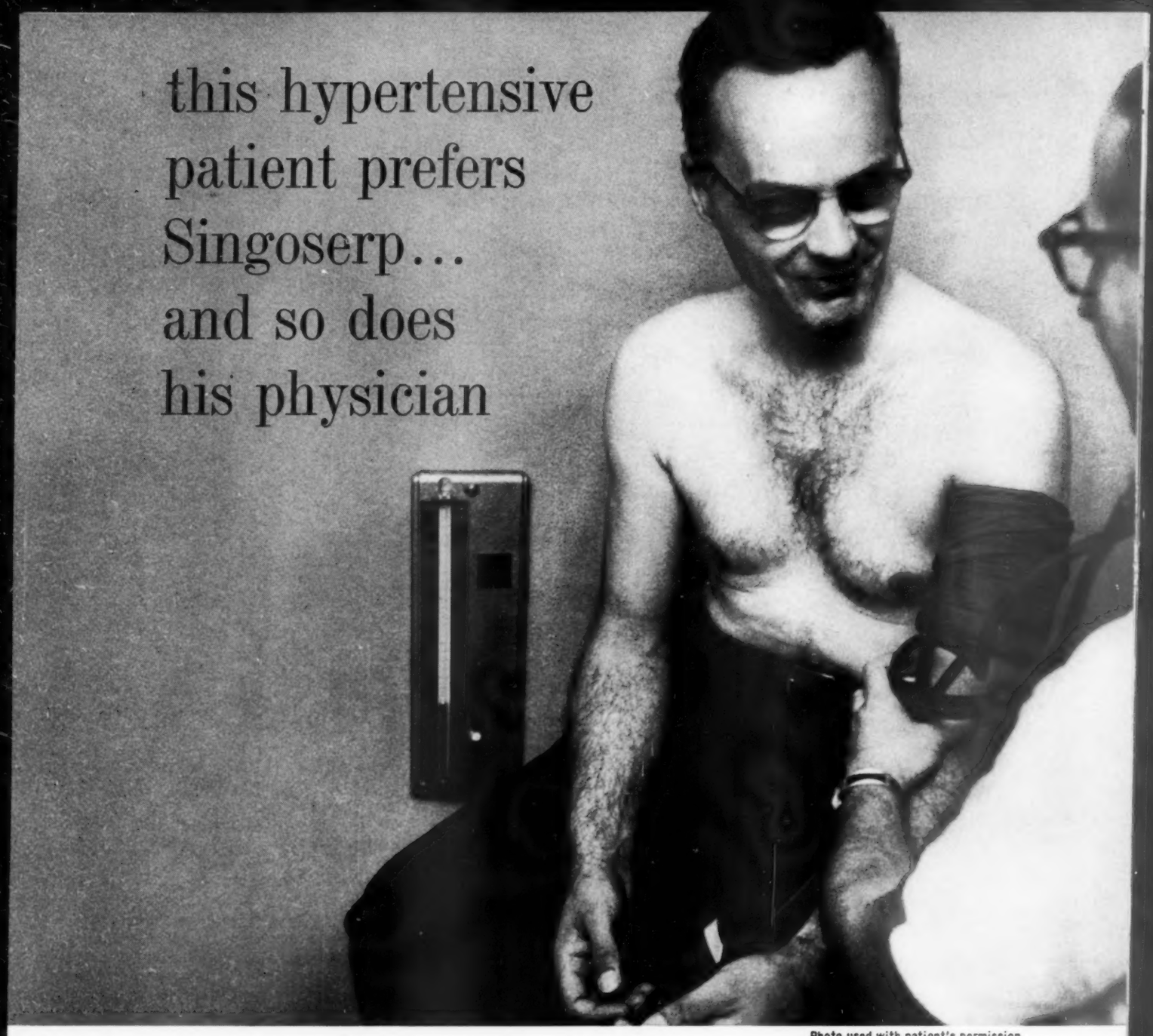


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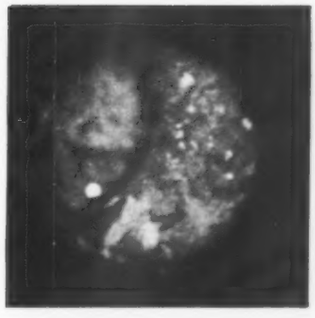
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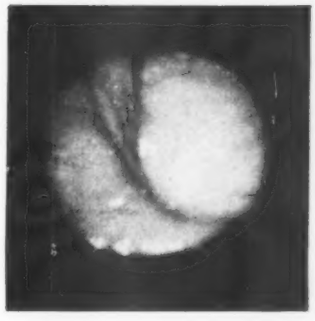
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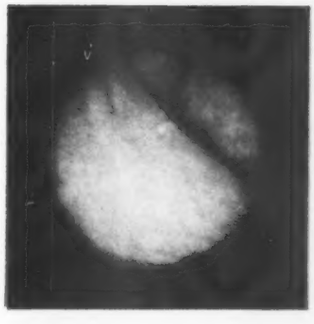
Proctoscopic view of the sigmoid in acute stage of ulcerative colitis



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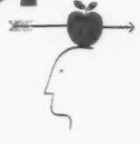
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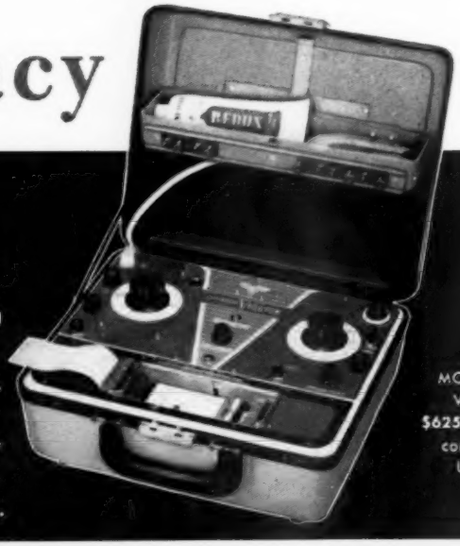
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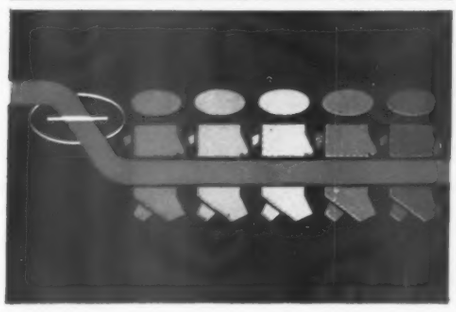


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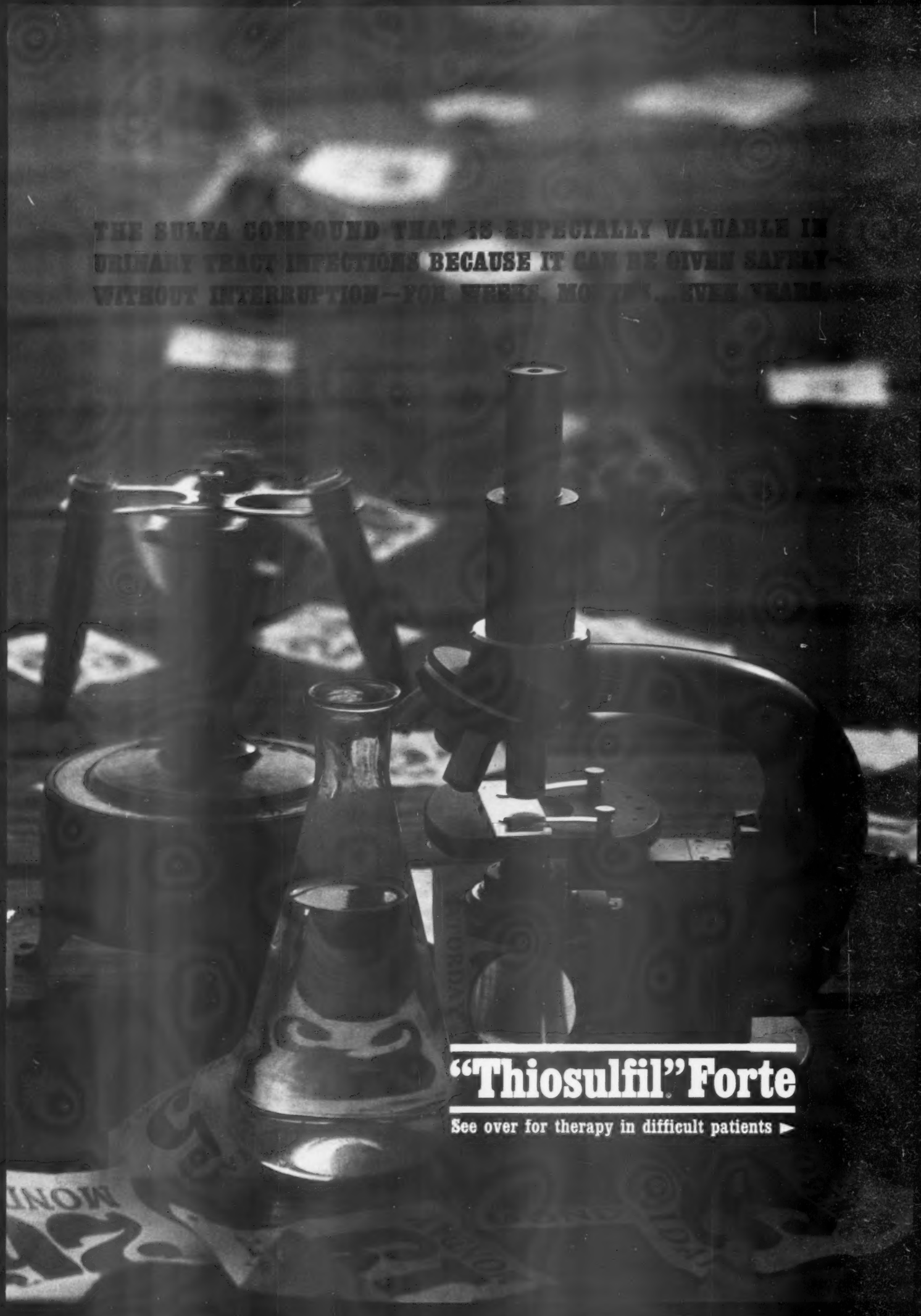
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HOW TO IMPROVE THE PROGNOSIS IN THE DIFFICULT PATIENT WITH URINARY TRACT INFECTION: Proof of effectiveness and record of safety in long term therapy are two important factors in the selection of a sulfa, particularly when the infection is stubborn and recurrent; occurs during pregnancy; in prostatitis; in patients with indwelling catheters; when stasis is a potential cause of ascending infection. "Thiosulfil" Forte is specially valuable in the treatment of problem patients with urinary tract infection as demonstrated by years of clinical experience.

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In acutely infected patients: Results of seven years' clinical experience:[1] Bourque's report covers 3,057 patients treated with "Thiosulfil" for upper and lower urinary tract infections. The causative organisms were E. Coli, Pseudomonas, Klebsiella, Enterococcus, Staphylococcus, Alcaligenes fecalis, and Proteus.

The results obtained were 76 per cent excellent; 11 per cent fair. In cystitis of short duration and without urinary obstruction 100 per cent good results were reported. average dosage: 3 Gm./day for 2 weeks

in pathologic conditions that cannot be cured 38 cases of chronic urinary tract infection:[2] "The cause of the infection in 25 cases was residual urine due to lower urinary tract disease, which for some reason could not be eliminated, such as prostatic carcinoma or hypertrophy (16 cases), vesical diverticulum or hypotonia (6 cases). Chronic upper urinary tract infection was present in 22 cases, some of which were secondary to the lower tract obstructive lesions."

"The results of treatment were as follows: Good, 17 cases, urine became clear and symptoms subsided while under treatment; fair, 10 cases, infection reduced and symptoms became less or subsided; poor, 11 cases, no evident change in urine or symptoms." initial dosage: 2 Gm./day

52 paraplegics with g.u. infections:[3] "Urinalysis reverted to normal in 53 per cent of the 'Thiosulfil' group . . ."

"'Thiosulfil' was ineffective in only 7 per cent . . ." dosage: 2 Gm./day

RECORD OF SAFETY

Only these few side effects have been reported with "Thiosulfil." Out of 52 paraplegic cases . . . only one instance of dermatitis.[3] Out of 50 cases . . . mild reactions consisted of slight gastric distress (1); flatulence (3); rash (1); pruritus (1); transient crystalluria (2).[4] Out of 38 cases of chronic infection . . . mild reactions of: stomach and eye discomforts (1); dizziness (1); slight diarrhea (1).[2] Out of 100 cases . . . one reaction—nausea.[5] Out of 3,057 cases . . . 47 patients (1.6%) showed g.i. disturbances and 33 patients (1.1%) allergic reactions.[1] Out of 300 cases . . . one reaction (appetite loss and lassitude).[6] NO REPORTS OF: hemorrhagic dyscrasias, hematuria, anuria, agranulocytosis.

The Sulfa Compound Used Successfully Without Interruption for: one month;[3,4] more than 6 weeks;[2] 90 days;[5] 18 months;[3] 5 to 6 years.[7]

DOSAGE (Urinary Tract Infections)

TIME PERIOD	DOSE
First two weeks	3 Gm./day[1]
2 weeks to 3 months	2 Gm./day[3,4]
3 months or longer	0.5 Gm./day[7]

Suggested Range of Dosage: 1 or 2 tablets three or four times daily. Note: The usual precautions exercised with sulfonamides should be observed. Supplied: No. 786—Bottles of 100 and 1,000 scored tablets. Each tablet contains 0.5 Gm. sulfamethizole.

References—1. Bourque, J-P., and Gauthier, G-E.: Seven years' experience with sulfamethizole, to be published. 2. Barnes, R. W.: J. Urol. **71**:655 (May) 1954. 3. Cottrell, T. L. C., Rolnick, D., and Lloyd, F. A.: Rocky Mountain M. J. **56**:66 (Mar.) 1959. 4. Bourque, J-P., and Joyal, J.: Canad. M.A.J. **68**:337 (Apr.) 1953. 5. Hughes, J., Coppridge, W. M., and Roberts, L. C.: South. M. J. **47**:1082 (Nov.) 1954. 6. Goodhope, C. D.: J. Urol. **72**:552 (Sept.) 1954. 7. Hughes, J., Coppridge, W. M., and Roberts, L. C.: North Carolina M. J. **17**:320 (July) 1956.

THE SULFA COMPOUND THAT IS ESPECIALLY VALUABLE IN URINARY TRACT INFECTIONS BECAUSE IT CAN BE GIVEN SAFELY—WITHOUT INTERRUPTION—FOR WEEKS, MONTHS...EVEN YEARS.

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supplied: In bottles of 60 black-and-white scored tablets. Prescription only.

References: 1. Steigmann, F., **et al.:** Am. J. Gastroenterol. **33:**109 (Jan.) 1960. 2. Hock, C. W.: to be published. 3. Leming, B. H., Jr.: Clin. Med. **6:**423 (Mar.) 1959. 4. Data in Roerig Medical Department Files.

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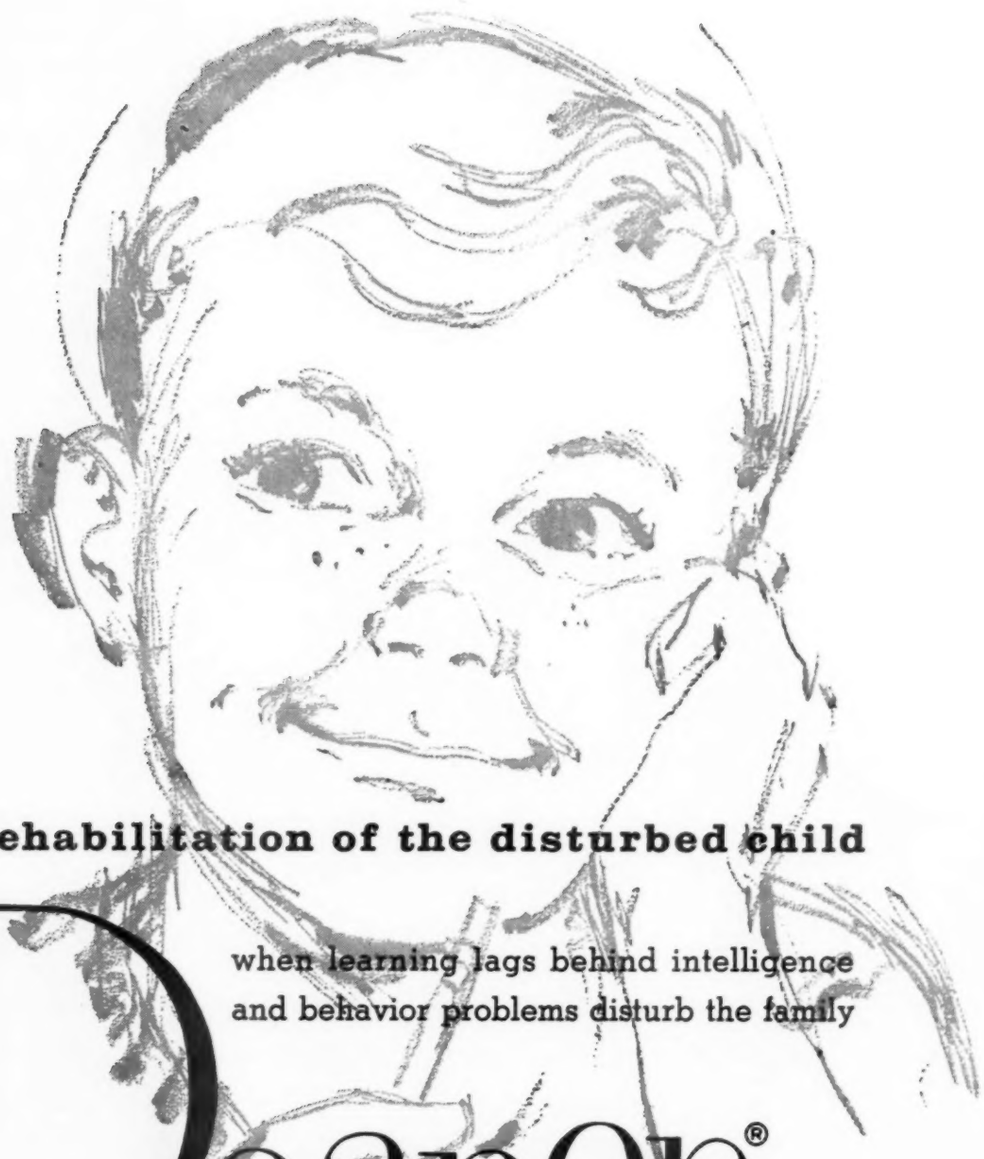
Dosage: 2 to 4 tablets t.i.d., with or after meals. Each tablet contains aluminum nicotinate Walker equivalent in activity to 500 mg. of nicotinic acid.

Supplied: Bottles of 100 and 1000.

References: 1. Tandowsky, R. M.: Personal communication. 2. Parsons, W. B.: *Curr. Therapeut. Res.* 2:137 (May) 1960. 3. Thompson, C. E.: Personal communication. 4. Biben, L. H.; Kurstin, W., and Protas, M.: Personal communication. 5. Hobbs, T. G.: Personal communication.

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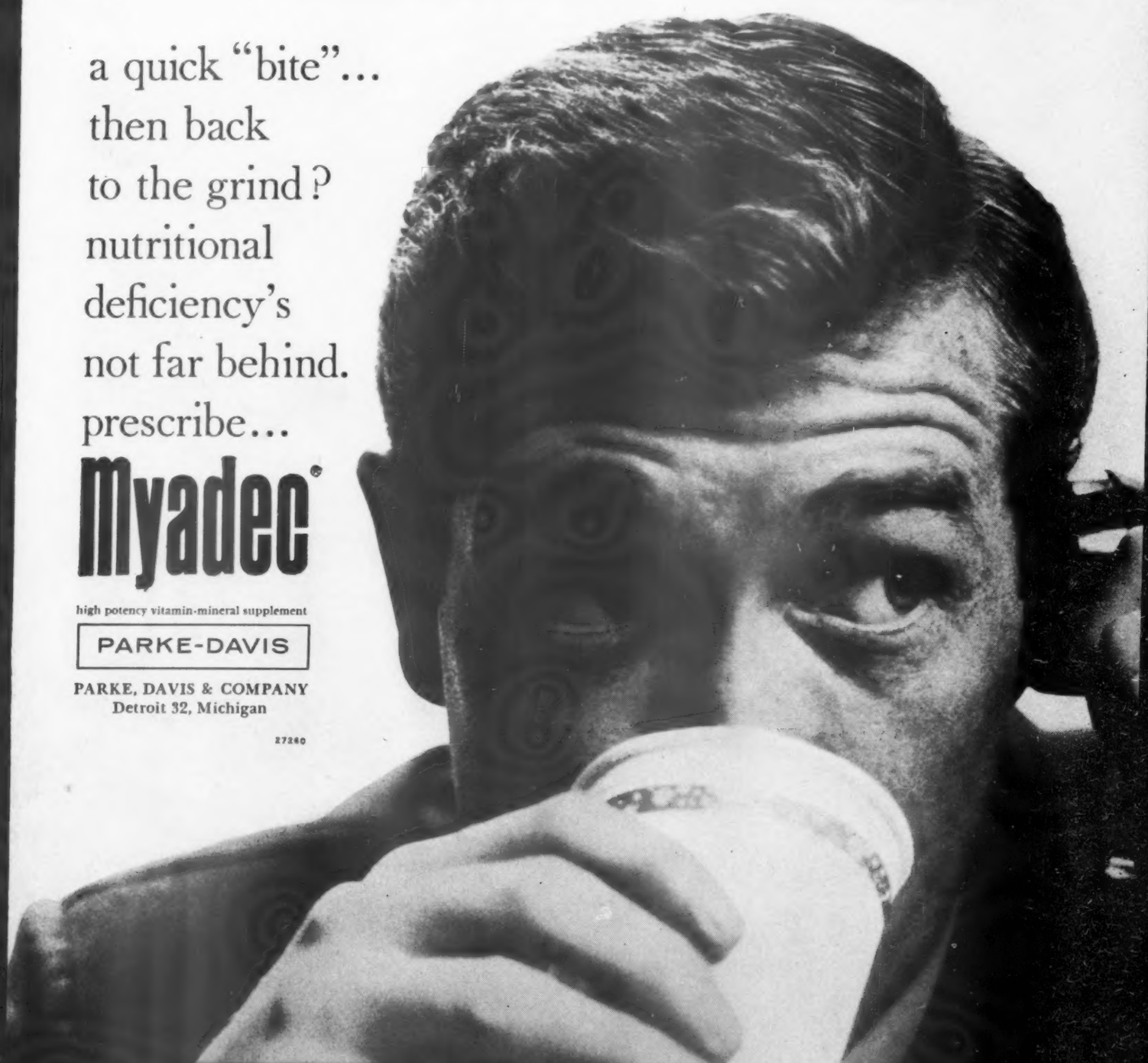
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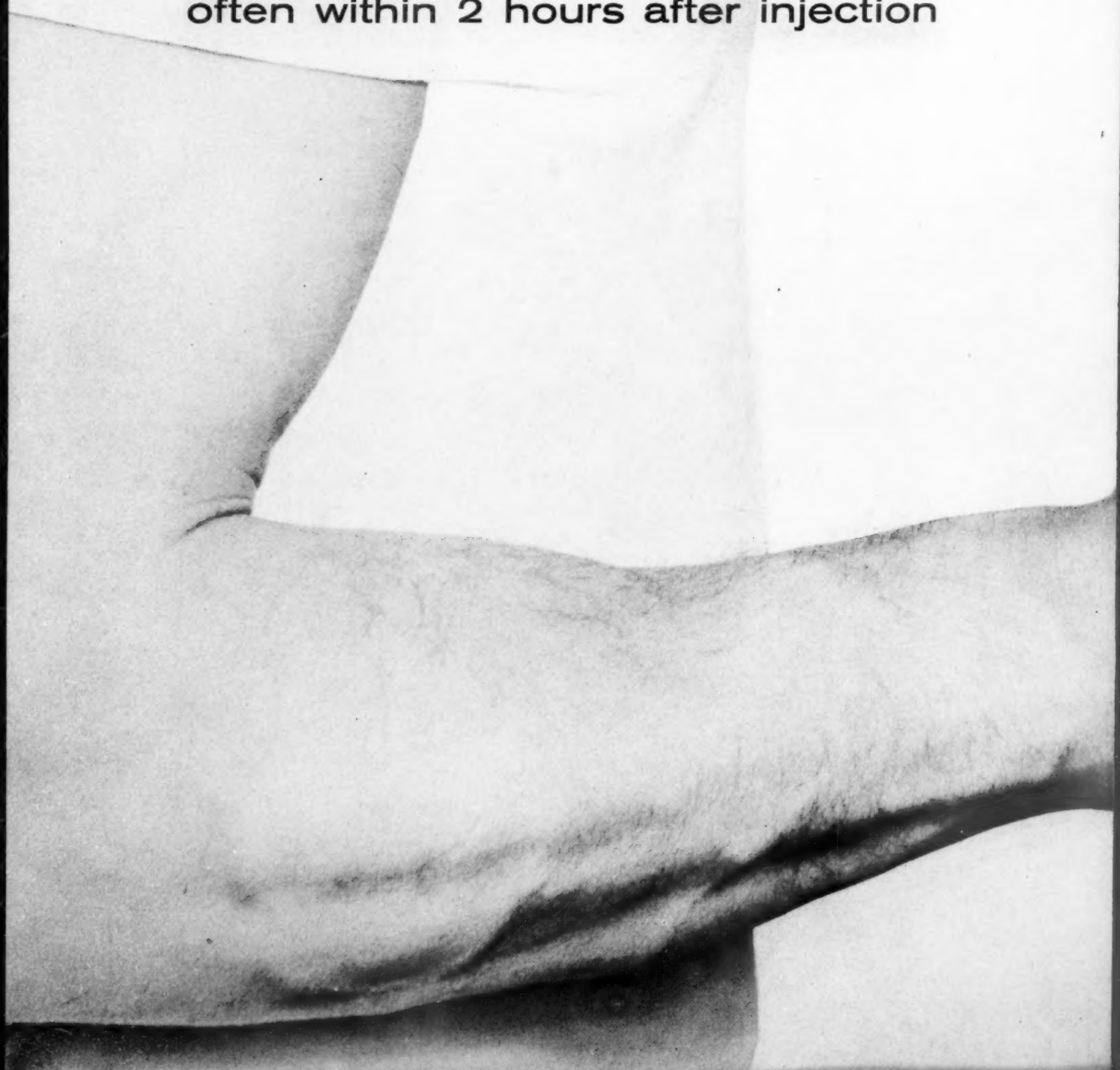
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1. Blumberg, N. *et al.*: Fed. Proc. 17:351, March 1958. **2.** Boyd, L. J. *et al.*: Am. J. Cardiol. 3:229, Feb. 1959. **3.** Brick, H. *et al.*: J. Social Therapy 4:190, 1958. **4.** Bulla, J. D. *et al.*: Am. Pract. & Digest Treat. 10:1961, Nov. 1959. **5.** Ewing, J. A. and Haizlip, T. M.: Am. J. Psychiat. 114:835, March 1958. **6.** Friedman, A. P.: Ann. N. Y. Acad. Sc. 67:822, May 9, 1957. **7.** Greenberg, L. A. *et al.*: Ann. N. Y. Acad. Sc. 67:816, May 9, 1957. **8.** Holliday, A. R.: Northwest Med. 58:837, June 1959. **9.** Hollister, L. E. *et al.*: Dis. Nerv. System 17:289, Sept. 1956. **10.** Laird, D. M. *et al.*: Dis Nerv. System 18:346, Sept. 1957.

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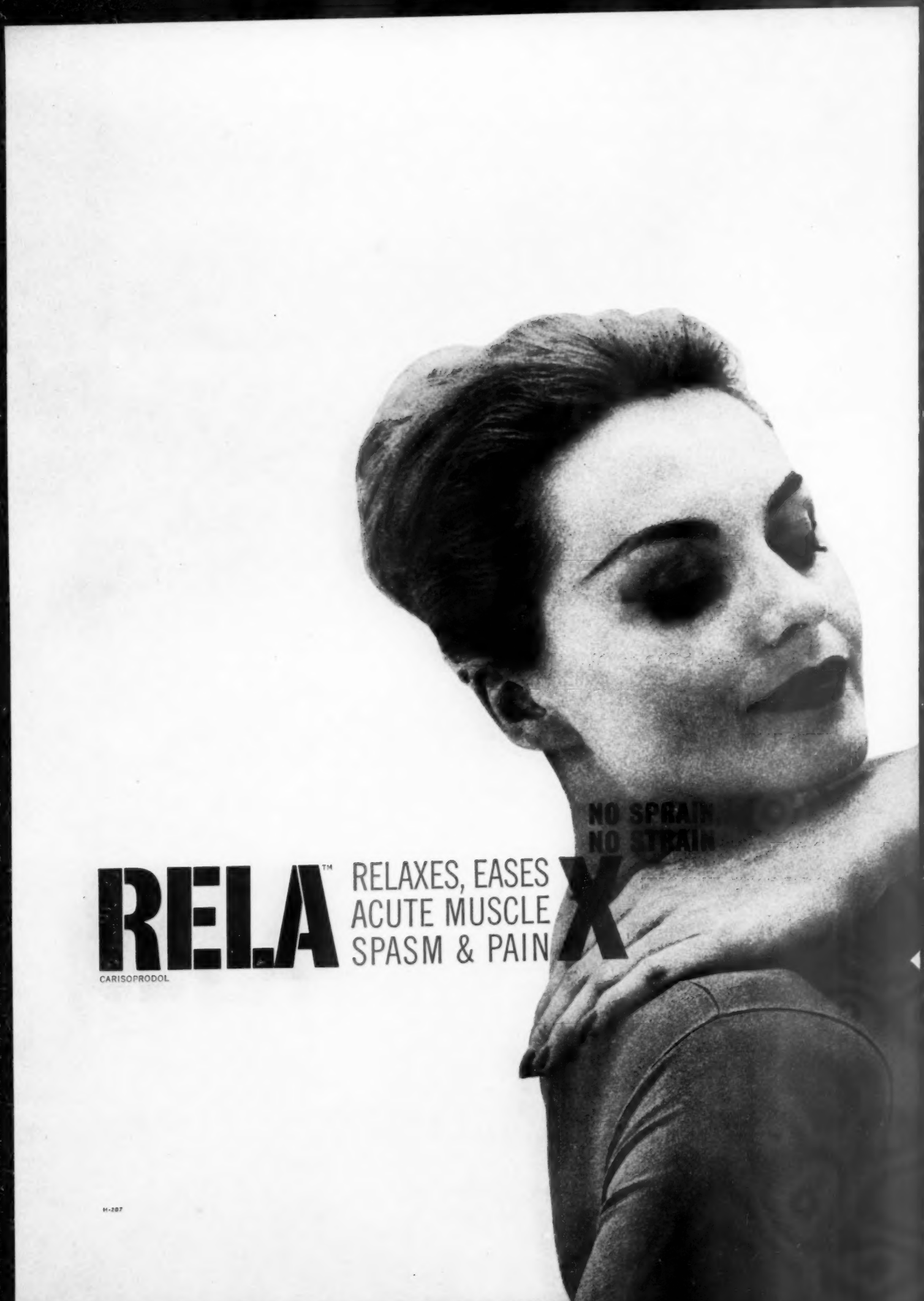
..[double-blind]

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Bibliography: 1. Ostrowski, J. P.: Orthopedics 2:7 (Jan.) 1960. 2. Kestler, O. C.: J. A. M. A. 171:2039 (April 30) 1960. 3. Frankel, K.: Paper presented at Scientific Meeting, New York State Society of Industrial Medicine, Inc., New York, Sept. 30, 1959.

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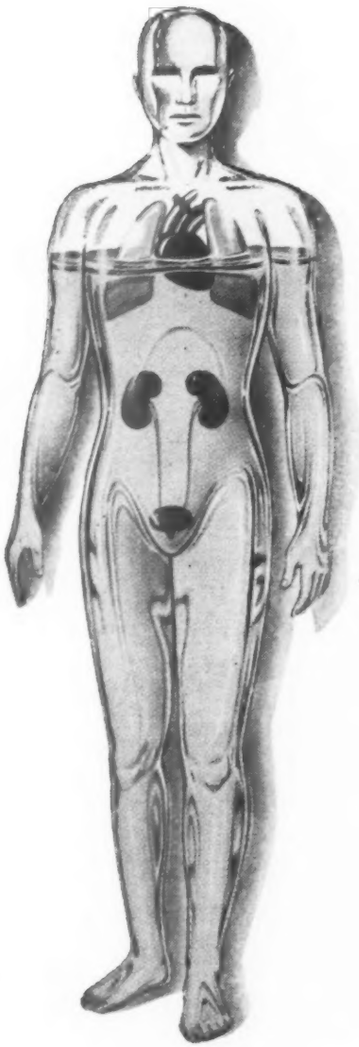
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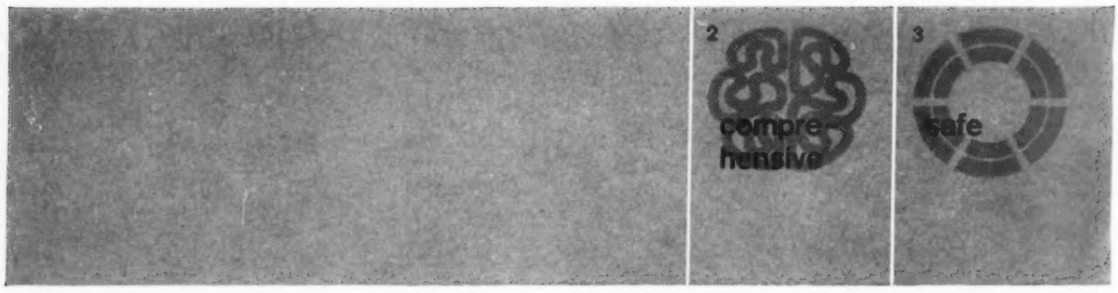
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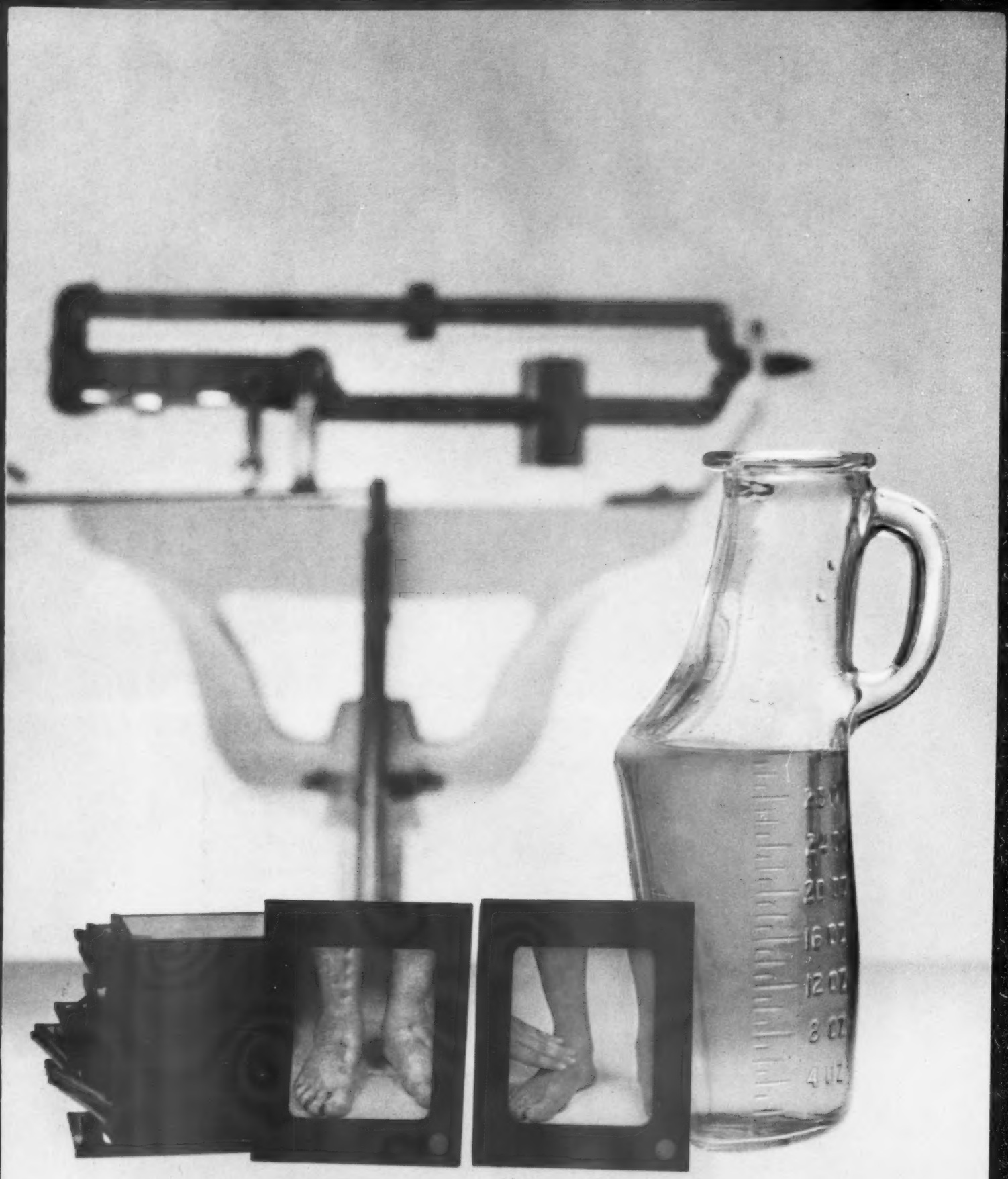
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for the treatment of anxiety & tension without causing drowsiness

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Supplied: 200 mg. yellow scored tablets, and 100 mg. pink tablets, each in bottles of 100 and 500.

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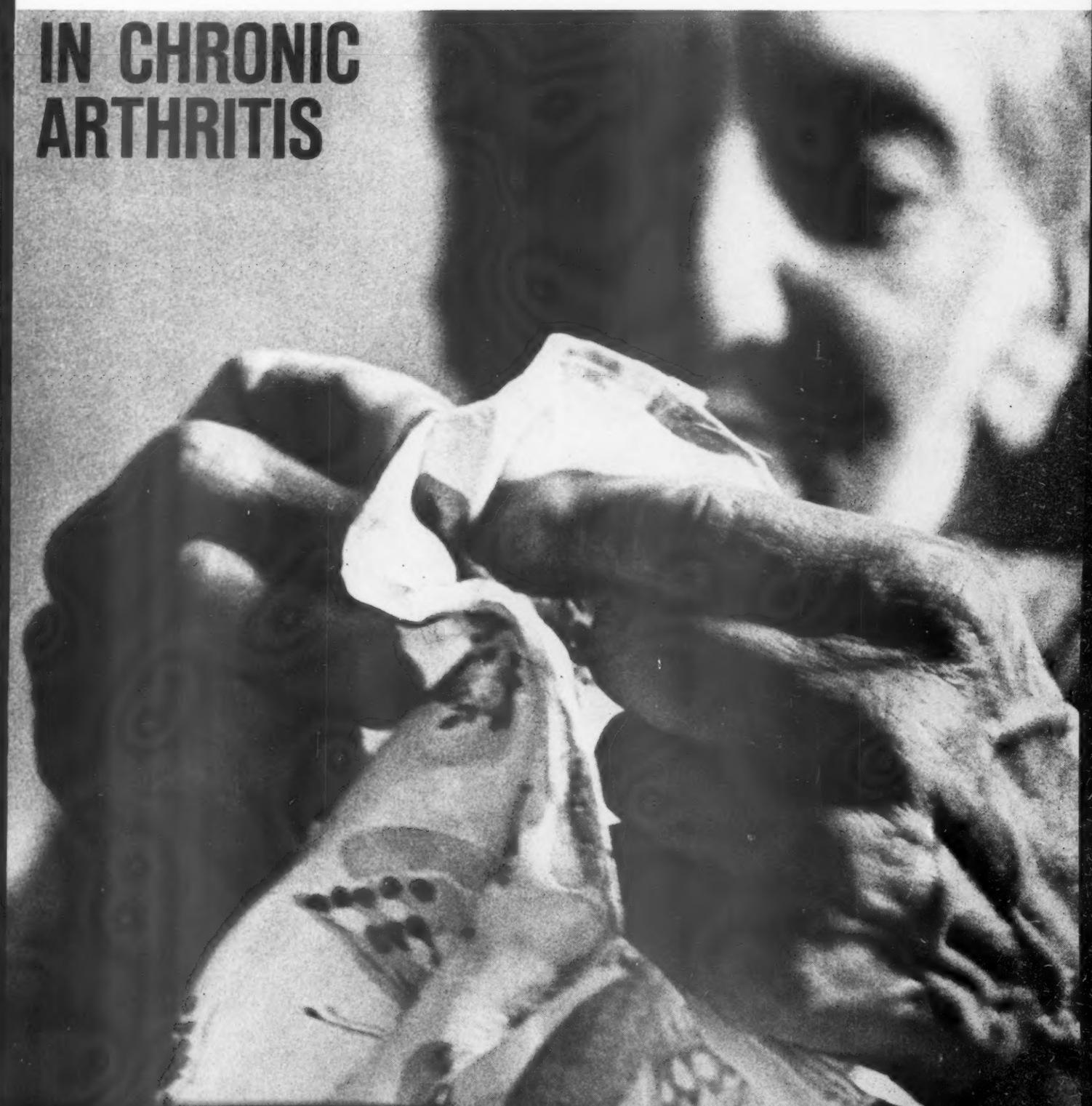
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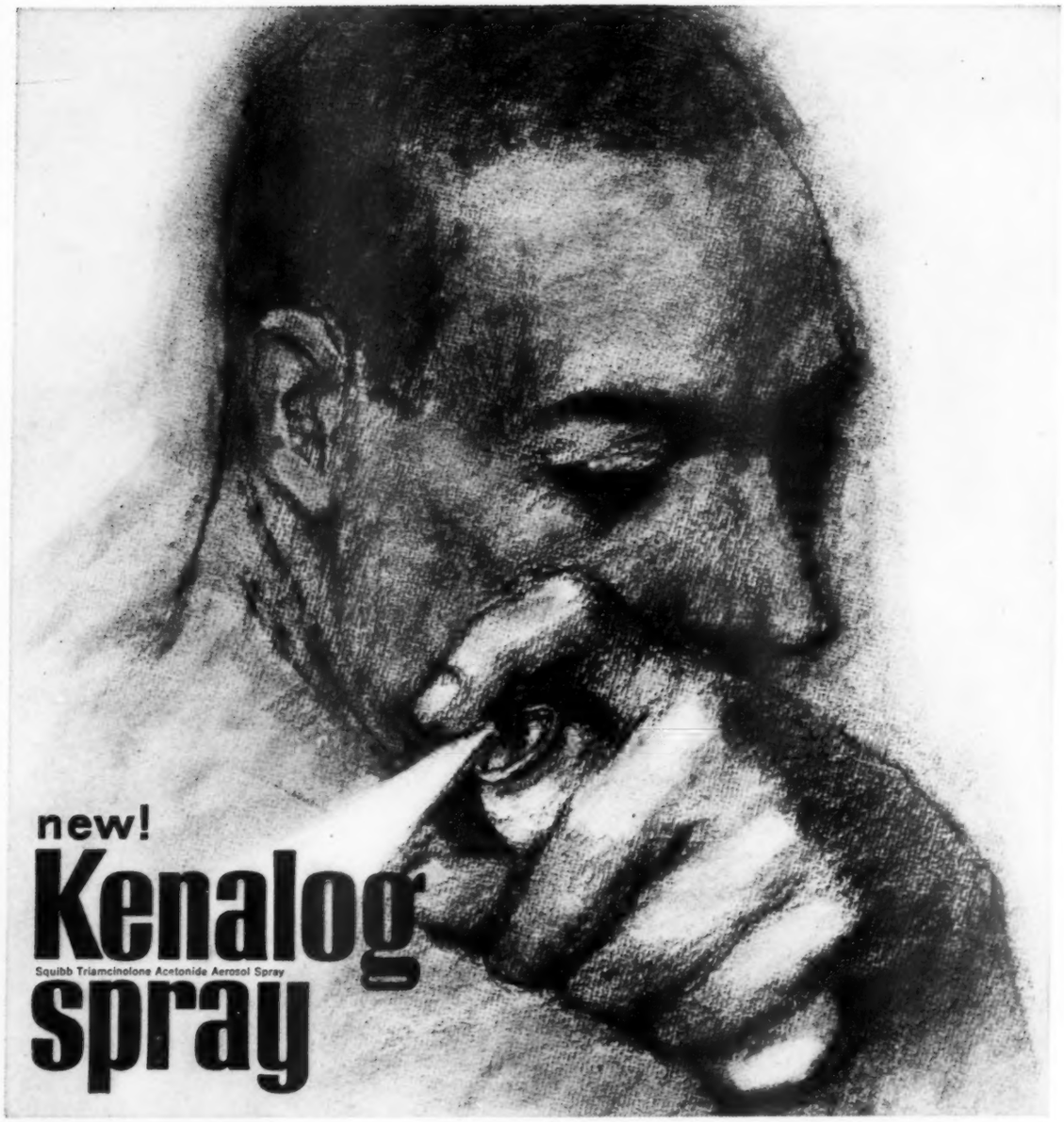
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superior topical corticosteroid

In convenient aerosol spray—for the treatment of dermatoses, particularly in out-of-reach problem areas—a fresh approach to therapy

- the superior anti-inflammatory effect of Kenalog[1-7] provides anti-inflammatory, antiallergic, and antipruritic relief in acute, exudative, weeping lesions, even in extensive, out-of-reach problem areas.
- minimal local irritation and less chance of local contamination.
- metabolic studies show electrolyte disturbance does not occur when Kenalog is applied topically.[1, 4, 5]
- easy to apply, gives broad, even coverage, and permits observation of lesions as they heal.

Indications: Atopic dermatitis, contact dermatitis, eczematous dermatitis, neurodermatitis, seborrheic dermatitis, insect bites, pruritus ani and vulvae, lichen simplex chronicus, exfoliative dermatitis, stasis dermatitis, nummular eczema, sunburn.

Dosage: Apply the spray to the affected areas from a distance of 3 to 6 inches, t.i.d. or q.i.d. A 3-second spray (delivering approximately 0.1 mg. of triamcinolone acetonide) covers an area about the size of the hand. *Cover the eyes when using Kenalog Spray on or near the face.*

Supply: Kenalog Spray in 50 and 150 Gm. containers of 3.3 mg. and 10 mg. triamcinolone acetonide respectively. Also available — Kenalog Cream (0.1%), Kenalog Ointment (0.1%) and Kenalog Lotion (0.1%).

References: 1. Reports to the Squibb Institute for Medical Research. 2. Howell, C. M.: Squibb Clin. Res. Notes *1*:5 (Oct.) 1958. 3. Goodman, J. J.: Squibb Clin. Res. Notes *1*:1 (Oct.) 1958. 4. Smith, J. G., Jr.; Zawisza, R. J., and Blank, H.: Squibb Clin. Res. Notes *1*:6 (Oct.) 1958. 5. Fitzpatrick, T. B.; Crowe, F. W., and Walker, S. A.: Squibb Clin. Res. Notes *1*:1 (Oct.) 1958. 6. Lerner, A. B.: Squibb Clin. Res. Notes *1*:2 (Oct.) 1958. 7. Robinson, R. C. V.: Bull. School of Med., U. Maryland 43:54 (July) 1958.

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B_{12} AND FOLIC ACID

AGAINST

MOUNTING EVIDENCE



Individually, folic acid and B_{12} fill important clinical roles.[1] But, increasing evidence indicates that multivitamins containing folic acid may obscure the diagnosis of pernicious anemia.[2-7] And vitamin B_{12}, in indiscriminate and unnecessary usage[5-8] is likewise blamed for this diagnostic confusion.[7]

Both folic acid and B_{12} have been omitted from Adabee, in recognition of this growing medical concern. Also excluded are other factors which might interfere with concurrent therapy, such as, hormones, enzymes, amino acids, and yeast derivatives. Adabee supplies massive doses of therapeutically practical vitamins for use in both specific and supportive schedules in illness and stress situations. Thus, new Adabee offers the therapeutic advantage of sustained maximum multivitamin support without the threat of symptom-masking.

references: 1. Wintrobe, M. M., *Clinical Hematology*, 3rd ed., Phila., Lea & Febiger, 1952, p. 398. 2. Goodman, L. S. and Gilman, A., *The Pharmacological Basis of Therapeutics*, 2nd. ed., New York, Macmillan, 1955, p. 1709. 3. New Eng. J.M., Vol. 259, No. 25, Dec. 18, 1958, p. 1231. 4. Frohlich, E. D., New Eng. J.M., 259:1221, 1958. 5. J.A.M.A., 169:41, 1959. 6. J.A.M.A., 173:240, 1960. 7. Goldsmith, G. A., American J. of M., 25:680, 1958. 8. Darby, W. J., American J. of M., 25:726, 1958.

ADABEE®

Each yellow, capsule-shaped tablet contains:

Vitamin A	25,000 USP units
Vitamin D	1,000 USP units
Thiamine mononitrate (B_1)	15 mg.
Riboflavin (B_2)	10 mg.
Pyridoxine HCl (B_6)	5 mg.
Nicotinamide (niacinamide)	50 mg.
Calcium pantothenate	10 mg.
Ascorbic acid (vitamin C)	250 mg.

ADABEE® M

Each green, capsule-shaped tablet contains Adabee plus nine essential minerals:

Iron	15.0 mg.	Zinc	1.5 mg.
Iodine	0.15 mg.	Potassium	5.0 mg.
Copper	1.0 mg.	Calcium	103.0 mg.
Manganese	1.0 mg.	Phosphorus	80.0 mg.
Magnesium	6.0 mg.		

indications: As dietary supplements for the deficiency states that accompany pregnancy and lactation, surgery, burns, trauma, alcohol ingestion, hyperthyroidism, infections, cardiac disease, polyuria, anorexia, cirrhosis, arthritis, colitis, diabetes mellitus, and degenerative diseases. Also in restricted diets, particularly peptic ulcer, in geriatrics, and in concurrent administration with diuretics and antibiotics.

dosage: One or more tablets a day, as indicated, preferably with meals.

new! ADABEE®

the multivitamin without B_{12} or folic acid

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Richmond 20, Virginia

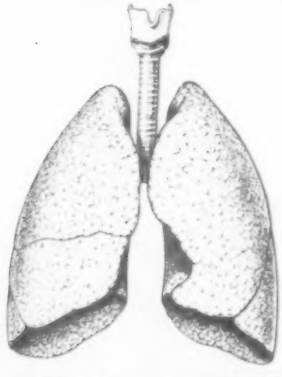
DECLOMYCIN NOTES:

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"Extra" activity, milligram for milligram[2-4] is the basis for outstanding clinical performance. Results of DECLOMYCIN therapy were satisfactory in a series of pneumonia cases, over half of which were complicated by pleural, suppurative, bronchial, or underlying structural lung problems.[1]



1. Duke, C. J.; Katz, S., and Donohoe, R. F.: Demethylchlortetracycline in the Treatment of Pneumonia, Read at Seventh Antibiotics Symposium, Washington, D. C., November 5, 1959. 2. Finland, M.; Hirsch, H. A., and Kunin, C. M.: Observations on Demethylchlortetracycline, Read at Seventh Antibiotics Symposium, Washington, D. C., November 5, 1959. 3. Hirsch, H. A., and Finland, M.: Antibacterial Activity of Serum of Normal Subjects After Oral Doses of Demethylchlortetracycline, Chlortetracycline and Oxytetracycline. **New England J. Med.** 260:1099 (May 28) 1959. 4. Lichter, E. A.; Sobel, S.; Spies, H. W.; Lepper, M. H. and Dowling, H. F.: Demethylchlortetracycline Therapy in Pneumonia, Scarlet Fever and Other Infections. **A.M.A. Arch. Int. Med.** 105:601 (Apr.) 1960.

CAPSULES, 150 mg.—PEDIATRIC DROPS, 60 mg./cc.—new cherry-flavored SYRUP, 75 mg./5 cc. tsp.

FULL ACTIVITY . . . LESS ANTIBIOTIC . . . SUSTAINED-PEAK CONTROL . . . "EXTRA-DAY" PROTECTION AGAINST RELAPSE

PRECAUTIONS: The use of antibiotics occasionally may result in overgrowth of nonsusceptible organisms. Constant observation of the patient is essential

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HYCOMINE®

Syrup

THE COMPLETE Rx FOR COUGH CONTROL

cough sedative | antihistamine
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■ relieves cough and associated symptoms in 15-20 minutes ■ effective for 6 hours or longer ■ promotes expectoration ■ rarely constipates ■ agreeably cherry-flavored

Each teaspoonful (5 cc.) of HYCOMINE* Syrup contains:

Hycodan®		
Dihydrocodeinone Bitartrate (Warning: May be habit-forming)	5 mg.	6.5 mg.
Homatropine Methylbromide	1.5 mg.	
Pyrilamine Maleate		12.5 mg.
Phenylephrine Hydrochloride		10 mg.
Ammonium Chloride		60 mg.
Sodium Citrate		85 mg.

Average adult dose: One teaspoonful after meals and at bedtime. May be habit-forming. Federal law permits oral prescription.

Literature on request

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One-half pound of Metrecal powder, the daily 900-calorie feeding, provides 70 grams of high-grade protein plus vitamins and minerals to meet or exceed all established minimum daily requirements. Metrecal itself *is* the diet—the *complete* diet.

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in uncomplicated overweight: In a twelve-day study of 100 patients[1] on the Metrecal 900-calorie program, the average total weight loss per subject was 6½ pounds (over ½ pound a day). In another study,[2] patients on the 900-calorie Metrecal program for two to thirty weeks showed a weight loss per patient of 3 to 5 pounds weekly during the initial weeks and 2 to 2½ pounds per patient per week thereafter.

in overweight complicated by illness: In a study of 42 overweight patients,[3] some with serious medical disorders such as arthritis, cardiovascular disease, diabetes mellitus and gout, the 900-calorie daily Metrecal program provided an average total weight loss of 6.3 pounds per patient during the first week. The investigator encountered no significant complications in the management of these patients.

excellent patient cooperation

All investigators[1,2,3] commented on excellent patient cooperation. This was attributed to the effective loss of weight, the satiety of Metrecal which satisfied hunger in a majority of patients, its simplicity of use—no calorie counting or menu planning required—and its palatability. No appetite depressants were required.

flexibility in use

When more than 900 calories are permitted, either the daily allotment of ½ pound of Metrecal may be increased or it may be used in conjunction with low-calorie foods. Metrecal may also be used for one or two meals a day or as the total diet two or three days a week.

easy to use

All patients do to make a full day's supply of Metrecal beverage is mix ½ pound of Metrecal powder with a quart of water. Or they may make a glassful at a time. For variety, Metrecal is available in Plain, Chocolate or Butterscotch flavors.

Weight-Control Guide for patient instruction is available from your Mead Johnson representative, or by writing to us, Evansville 21, Indiana.

references. (1) Antos, R. J.: Southwestern Med. *40*:695-697 (Nov.) 1959. (2) Tullis, I. F.: Initial Experience with a Simple Weight Control Formula, to be published. (3) Roberts, H. J.: Effective Long-Term Weight-Reduction—A Therapeutic Breakthrough, to be published.



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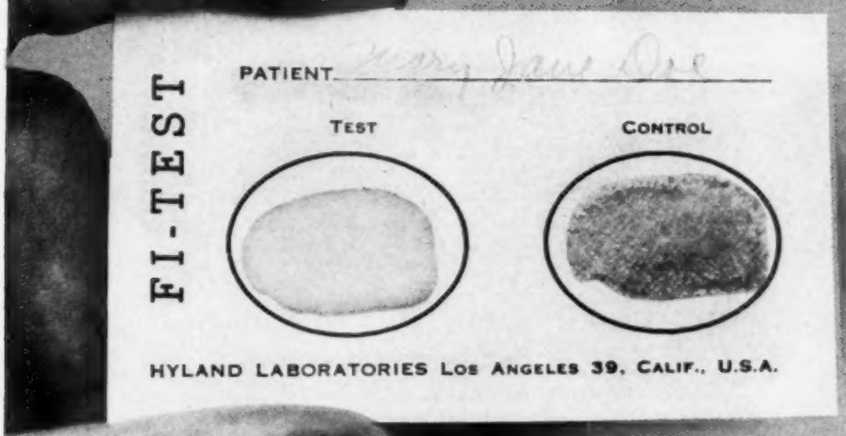
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FI-TEST indicates whether fibrinogen content is above or below 100 mg-%, the concentration considered critical. Easy-to-read results indicate promptly whether or not replacement fibrinogen is needed. (If reading shows a normal fibrinogen level, needless replacement therapy may be avoided and the physician is alerted to seek another explanation for continued bleeding.)

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VIRTUALLY NO DECREASE IN STAPHYLOCOCCAL SENSITIVITY

OVER AN 8-YEAR SPAN . . . TO

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(chloramphenicol, Parke-Davis)

An outstanding and frequently reported characteristic of CHLOROMYCETIN[1-8] "...is the fact that the very great majority of the so-called resistant staphylococci are susceptible to its action."[1] In describing their study, Rebhan and Edwards[2] state that "...only a small percentage of strains have shown resistance..." to CHLOROMYCETIN, despite steadily increasing use of the drug over the years.

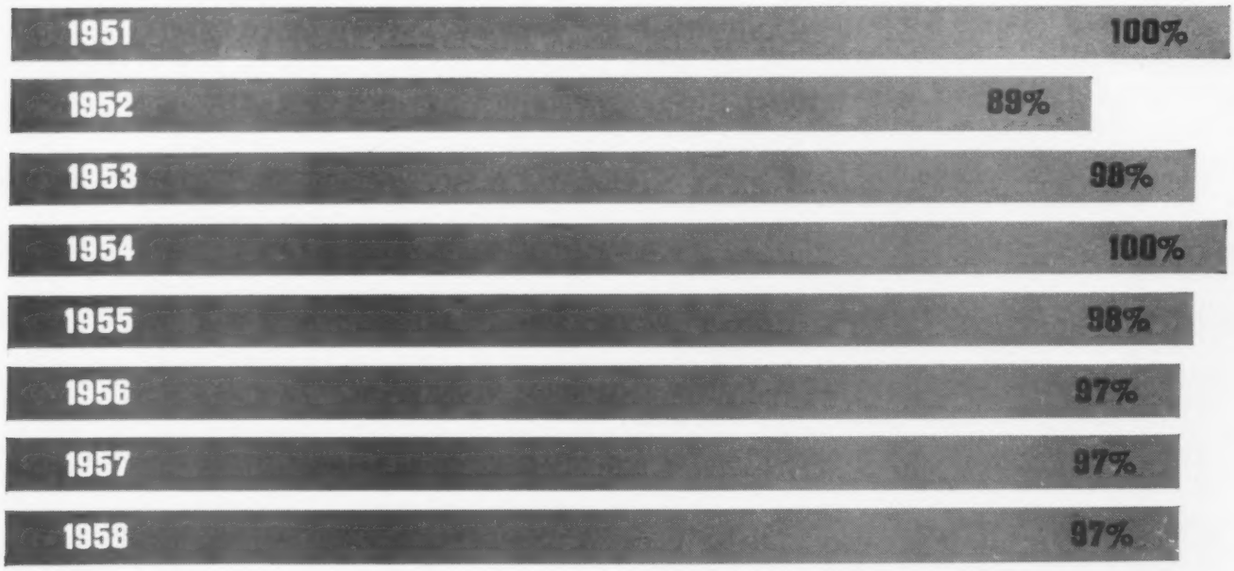
Fisher[3] observes: "The over-all average incidence of resistance, for the 31,779 strains [of staphylococci] through nine years was about 9%." Finland[4] reports that, while the proportion of strains resistant to several newer antibiotics has risen to between 10 and 30 per cent, such resistance to CHLOROMYCETIN "...has been rare even where this agent has been used extensively." Numerous other investigators concur in these findings.[5-8]

CHLOROMYCETIN (chloramphenicol, Parke-Davis) is available in various forms, including Kapseals® of 250 mg., in bottles of 16 and 100.

CHLOROMYCETIN is a potent therapeutic agent and, because certain blood dyscrasias have been associated with its administration, it should not be used indiscriminately or for minor infections. Furthermore, as with certain other drugs, adequate blood studies should be made when the patient requires prolonged or intermittent therapy.

References: (1) Welch, H., in Welch, H., & Finland, M.: Antibiotic Therapy for Staphylococcal Diseases, New York, Medical Encyclopedia, Inc., 1959, p. 1. (2) Rebhan, A. W., & Edwards, H. E.: *Canad. M. A. J.* **82**:513, 1960. (3) Fisher, M. W.: *Arch. Int. Med.* **105**:413, 1960. (4) Finland, M., in Welch, H., & Finland, M.: Antibiotic Therapy for Staphylococcal Diseases, New York, Medical Encyclopedia, Inc., 1959, p. 187. (5) Bercovitz, Z. T.: *Geriatrics* **15**:164, 1960. (6) Glas, W. W., & Britt, E. M.: Management of Hospital Injections, in Symposium on Antibacterial Therapy, Michigan & Wayne County Acad. Gen. Pract., Detroit, September 12, 1959, p. 7. (7) Staphylococcal Infections in Pediatrics, Scientific Exhibit, Commission on Professional and Hospital Activities, 108th Ann. Meet., A. M. A., Atlantic City, June 8-12, 1959. (8) Robinson, H. M., Jr.; Robinson, R. C. V., & Raskin, J.: *Postgrad. Med.* **27**:522, 1960.

IN VITRO SENSITIVITY OF PYOGENIC STRAINS OF STAPHYLOCOCCI TO CHLOROMYCETIN OVER A PERIOD OF EIGHT YEARS*

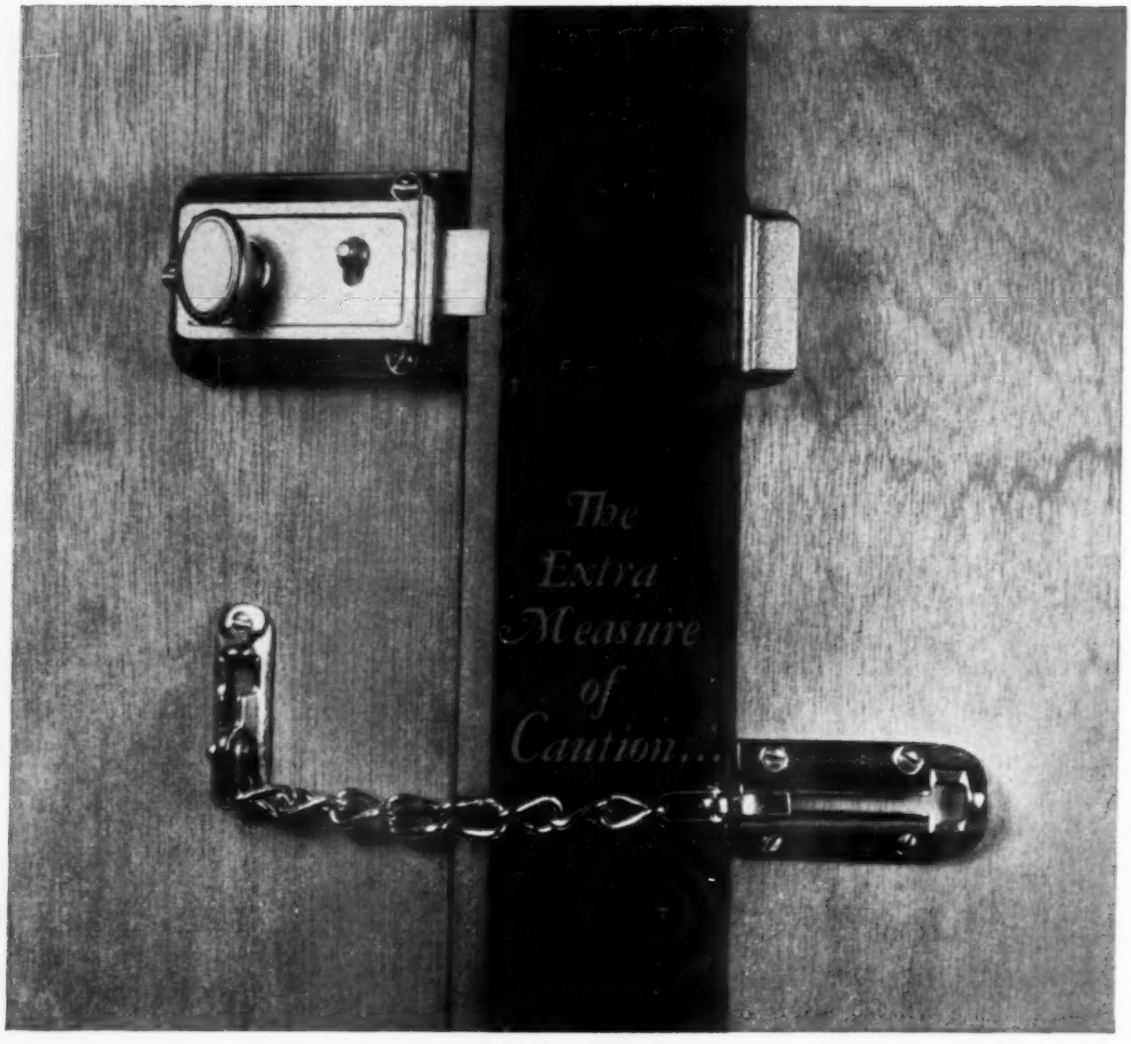


Statistics were gathered over almost a decade on 329 children with staphylococcal pneumonia; 1,663 sensitivity tests were performed.

*Adapted from Rebhan & Edwards.[3]

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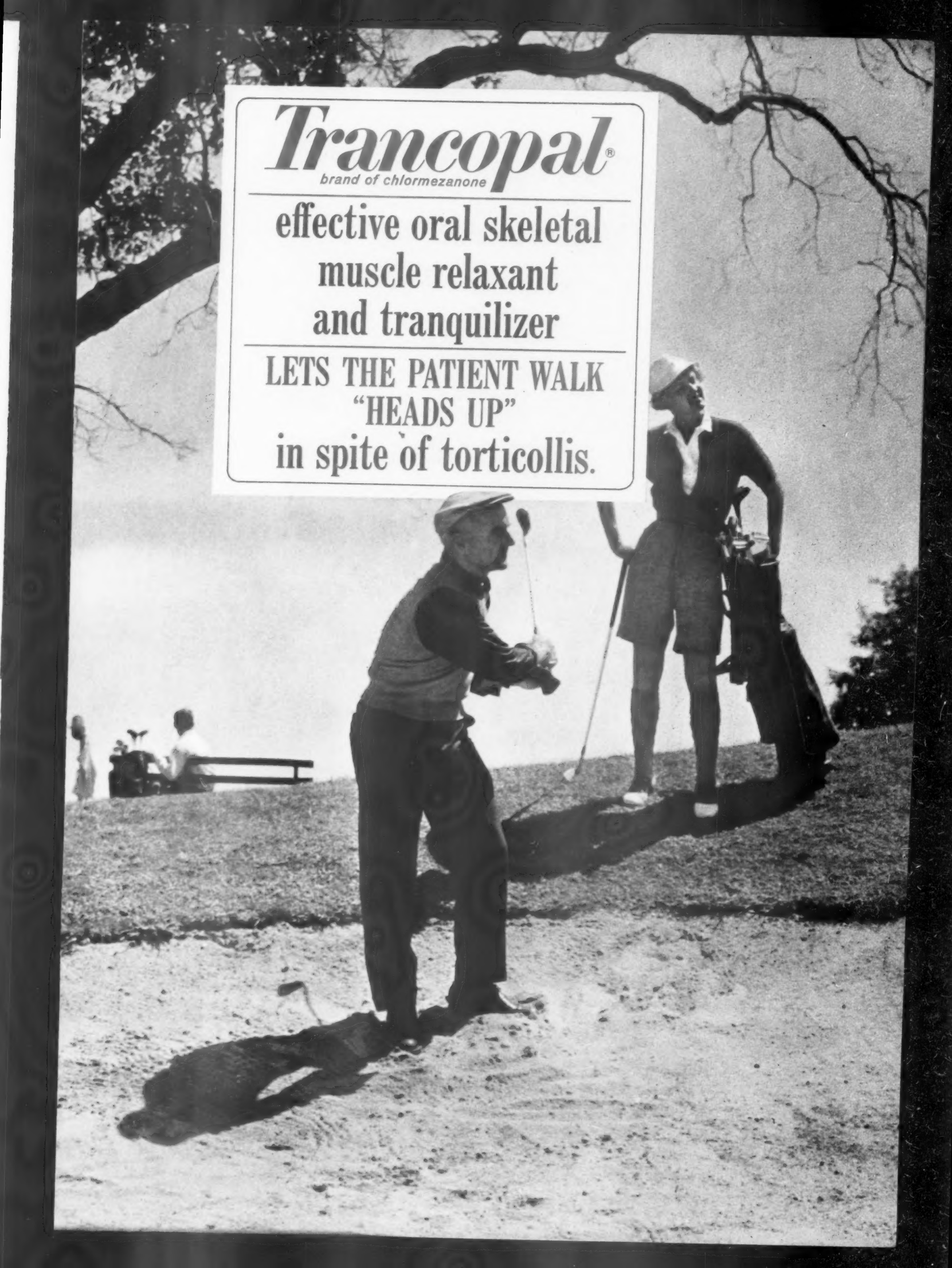
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LETS THE PATIENT WALK
"HEADS UP"
in spite of torticollis.



Trancopal
relieves pain and spasm associated with torticollis.

In a recent study by Ganz, Trancopal brought considerable improvement or very effective relief to 20 of 29 patients with torticollis.[1] "The patients helped by the drug," states Ganz, "were able to carry the head in the normal position without pain." Similarly, Kearney found that in 8 of 13 patients with chronic torticollis treated with Trancopal improvement was excellent to good. ". . . Trancopal is the most effective oral skeletal muscle relaxant and mild tranquilizer currently available."[2]

Lichtman, in a study of patients with various musculoskeletal conditions, noted that 64 of 70 patients with torticollis obtained excellent to good relief with Trancopal.[3]

In a comparative study of four central nervous system relaxants, Lichtman reports that 26 of 40 patients found Trancopal to be the most effective drug.[3]

1. Ganz, S. E.: *J. Indiana M.* 52:1134, July, 1959. 2. Kearney, R. I *Current Therap. Res.* 2:127, Ap 1960. 3. Lichtman, A. L.: *Kentu Acad. Gen. Pract. J.* 4:28, Oct., 19

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Clinical results with *Trancopal*®[2]

	Excellent	Good	Fair	Poor	Total
LOW BACK SYNDROMES					
Acute low back strain	25	19	8	6	58
Chronic low back strain	11	5	1	1	18
"Porters' syndrome"*	21	5	1	1	28
Pelvic fractures	2	1	—	—	3
NECK SYNDROMES					
Whiplash injuries	12	6	2	1	21
Torticollis, chronic	6	2	3	2	13
OTHER MUSCLE SPASM					
Spasm related to trauma	15	6	1	—	22
Rheumatoid arthritis	—	18	2	1	21
Bursitis	2	6	1	—	9
TENSION STATES	18	2	4	3	27
TOTALS	112 (51%)	70 (32%)	23 (10%)	15 (7%)	220 (100%)

*Over-reaching in lifting heavy bags resulting in sprain of upper, middle, and lower back muscles.

Dosage: **Adults, 200 or 100 mg. orally three or four times daily.**
Relief of symptoms occurs in from fifteen to thirty minutes and lasts from four to six hours.

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200 mg. (green colored, scored), bottles of 100.
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How new Dianabol rebuilt muscle tissue in this underweight, debilitated patient

Patient was weak and emaciated before Dianabol. R. C., age 51, weighed 160 pounds following surgery to close a perforated duodenal ulcer. His convalescence was slow and stormy, complicated by pneumonia of both lower lobes. Weak and washed out, he was considered a poor risk for further necessary surgery (cholecystectomy). Because a conventional low-fat diet and multiple-vitamin therapy failed to build up R. C. sufficiently, his physician prescribed Dianabol 5 mg. b.i.d.

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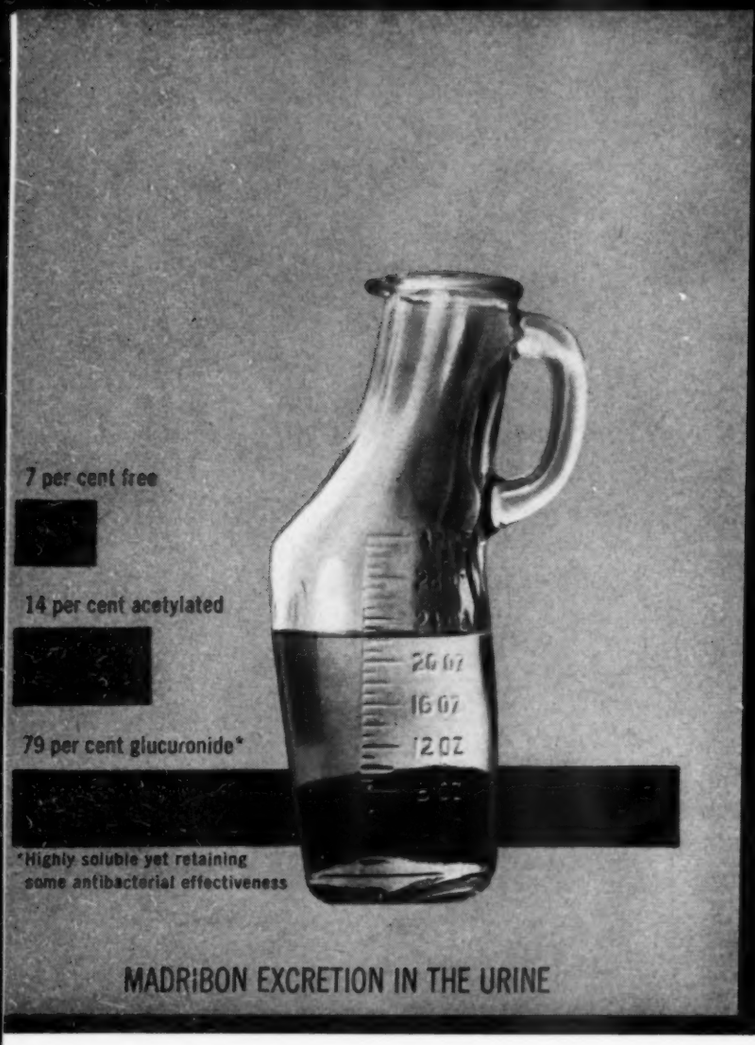
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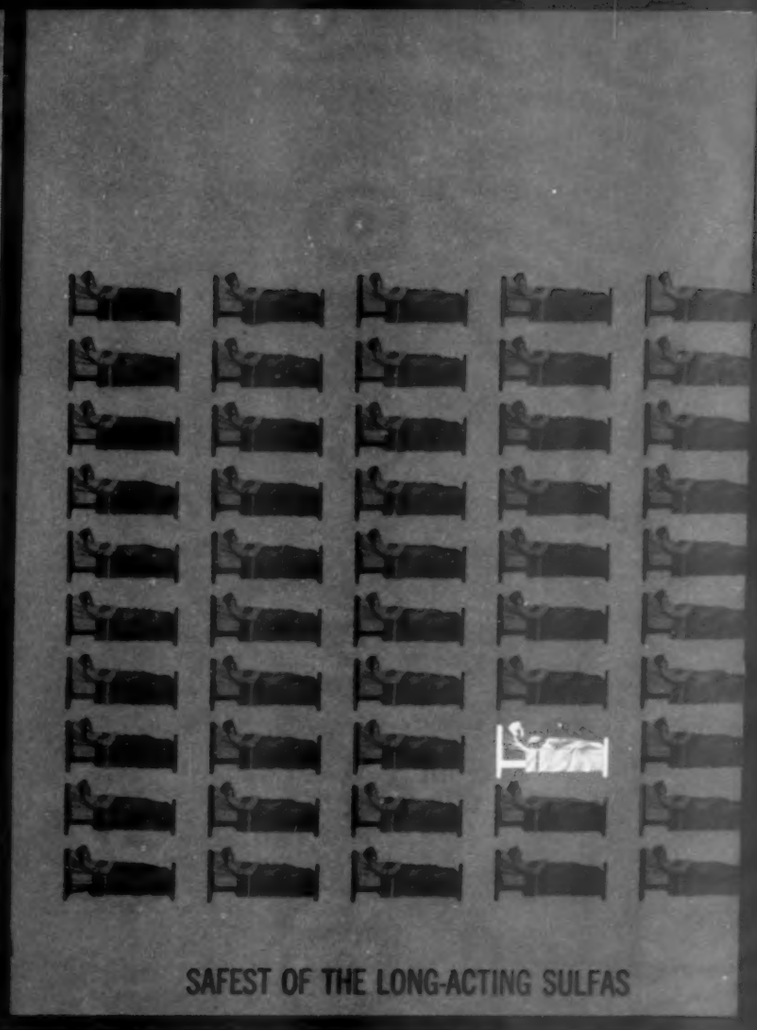
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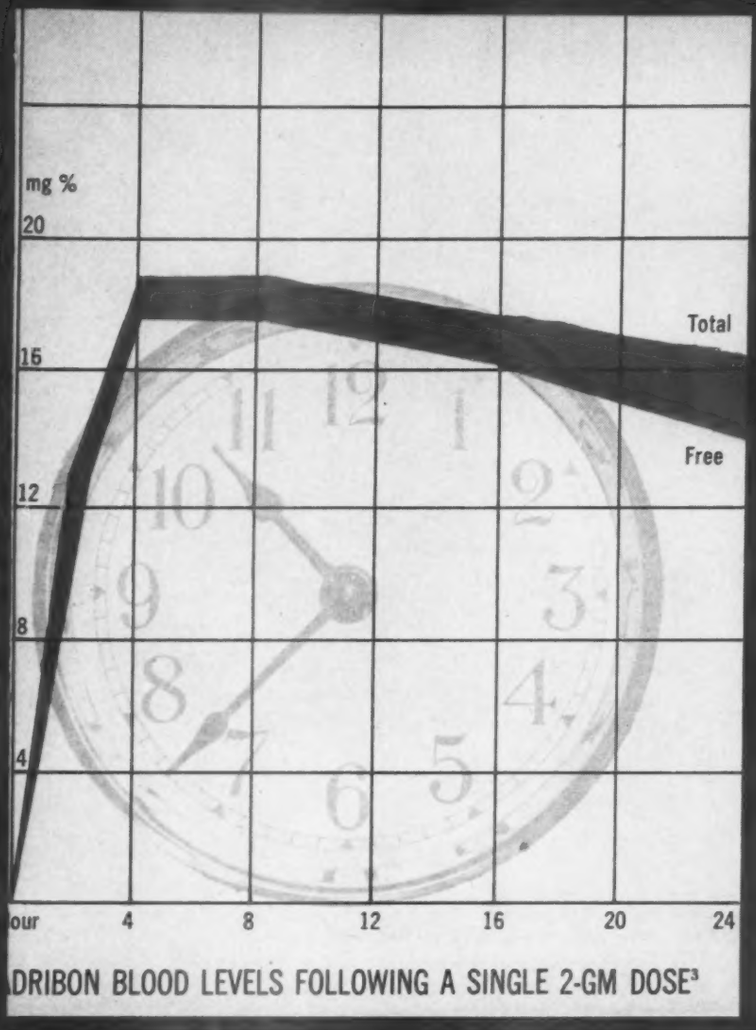
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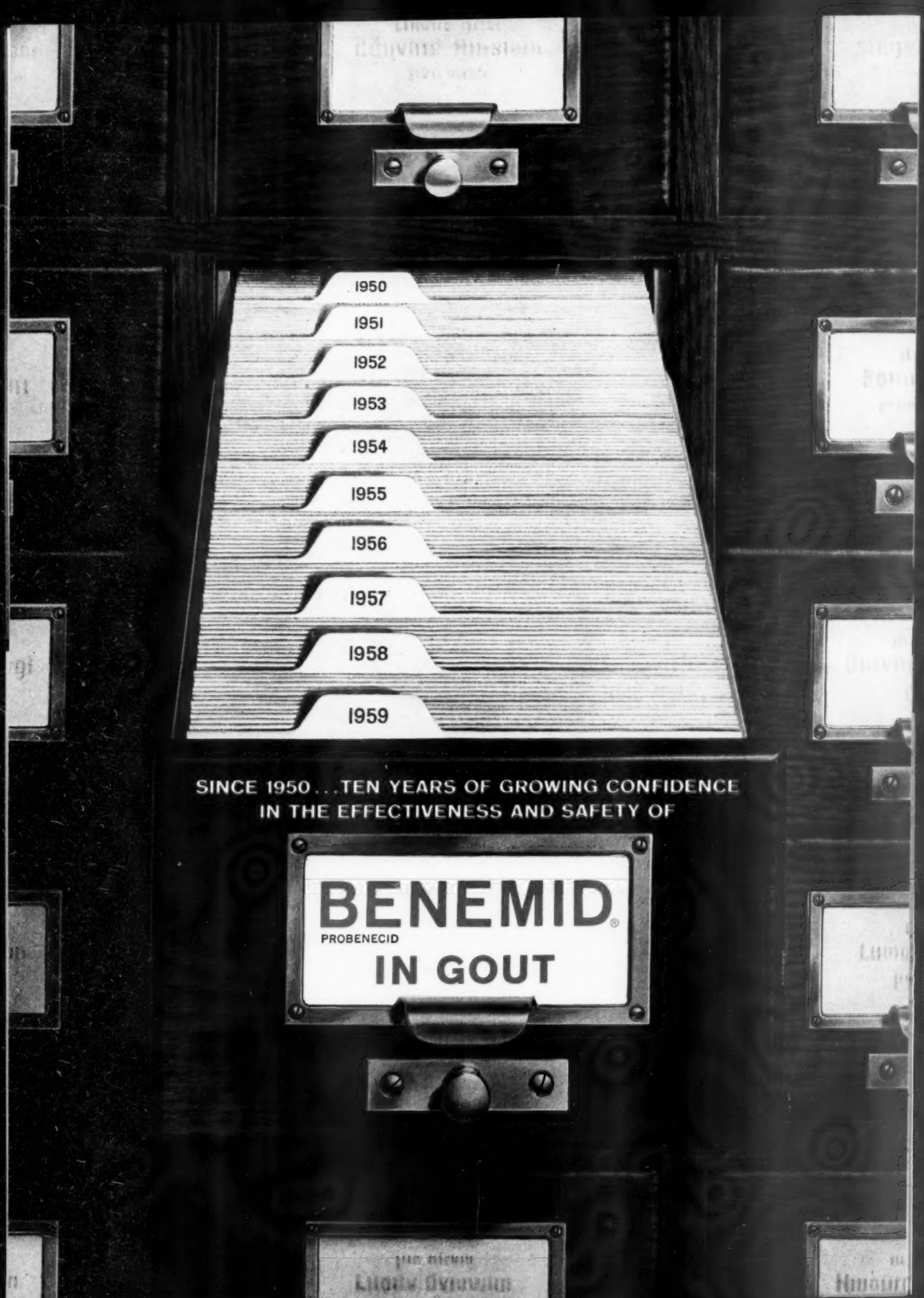


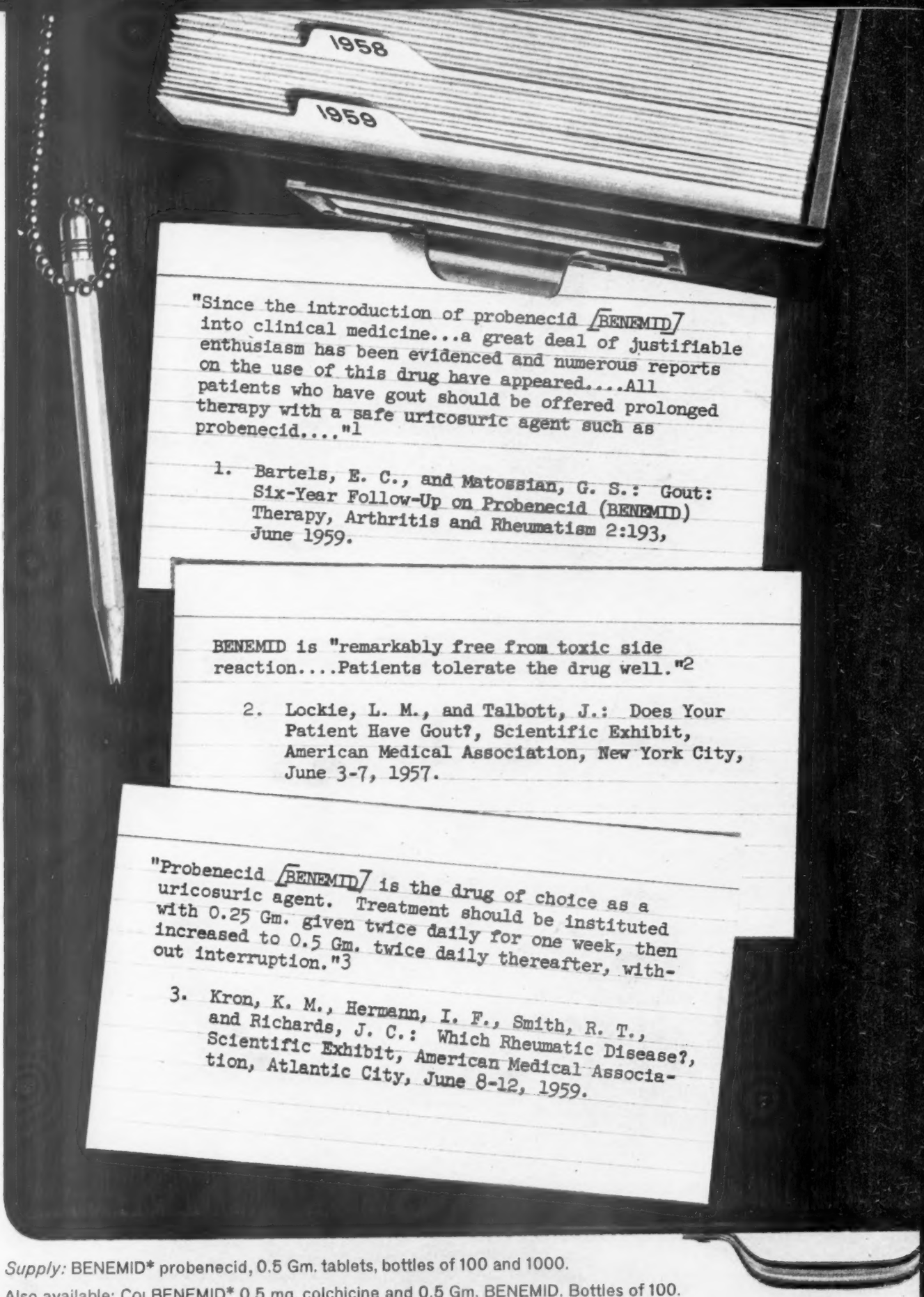
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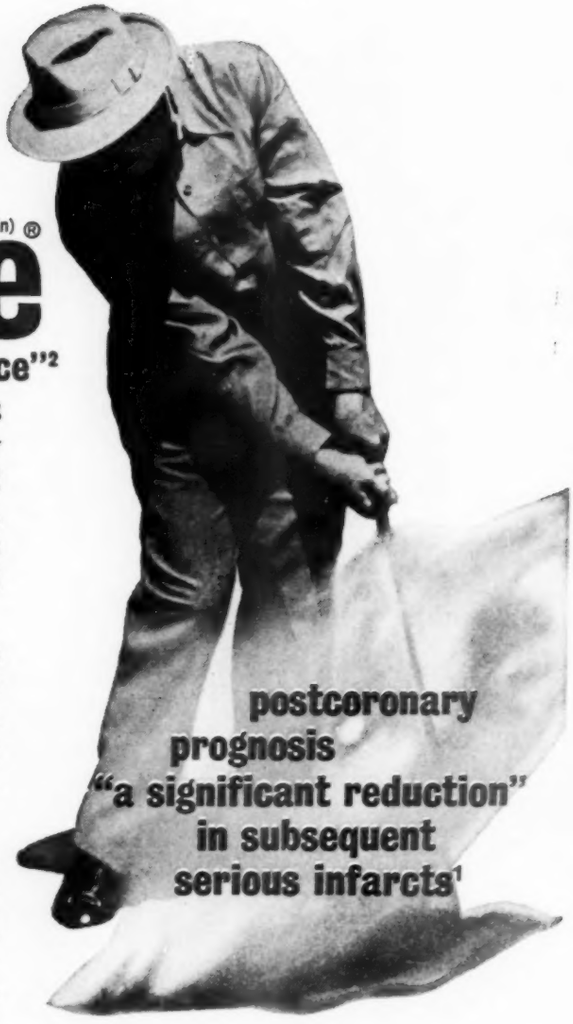
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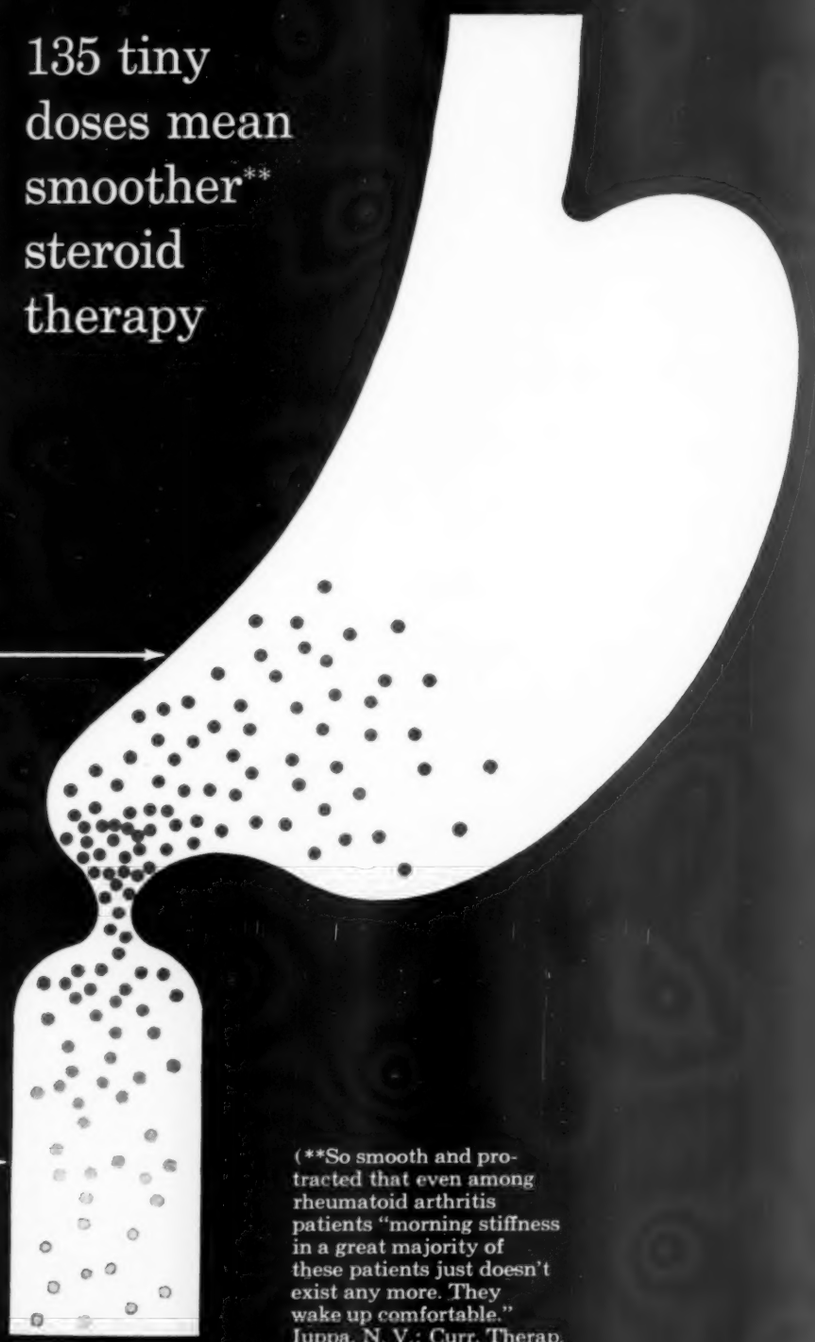
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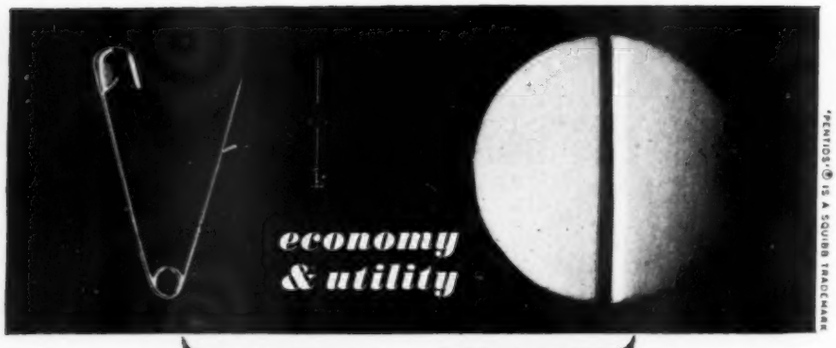
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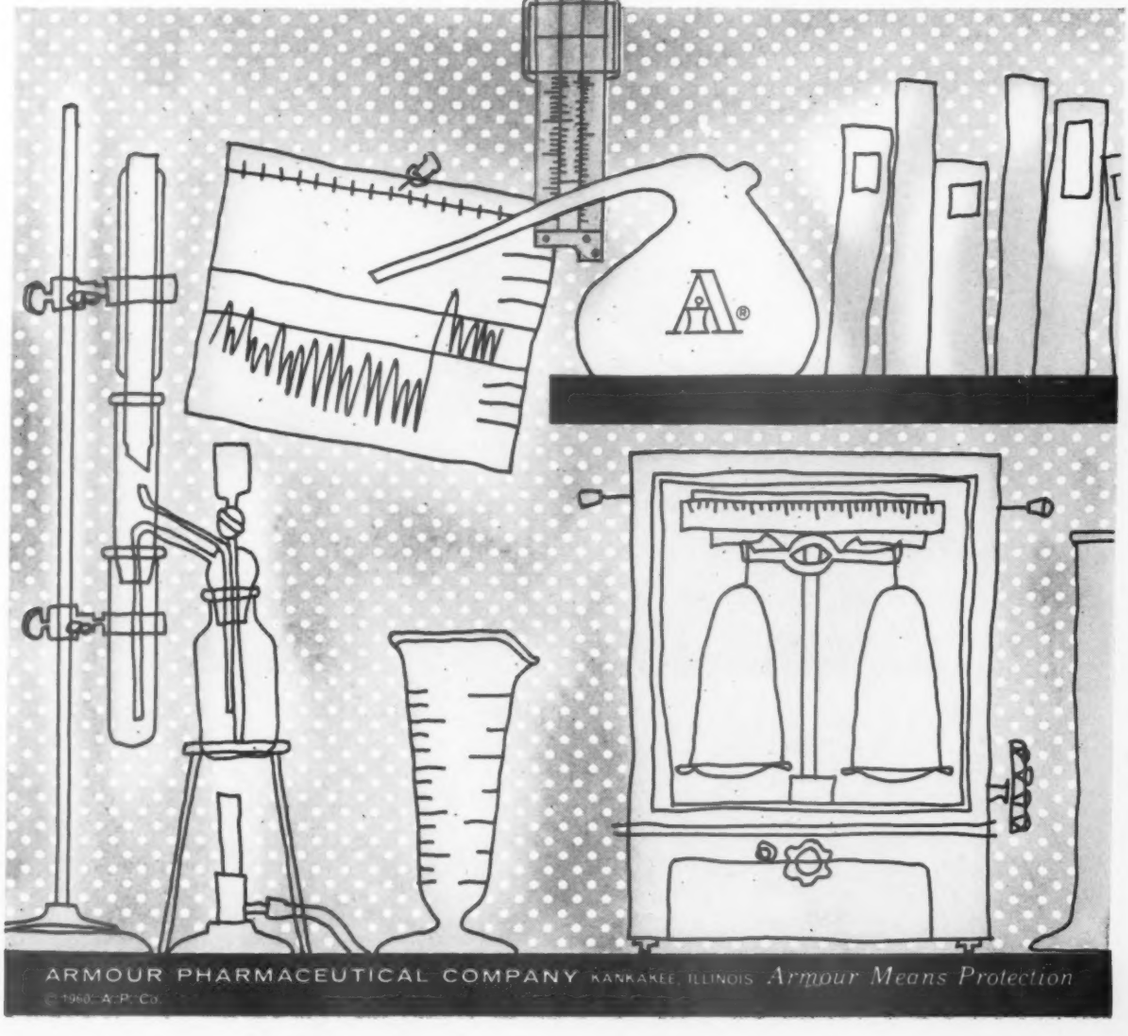
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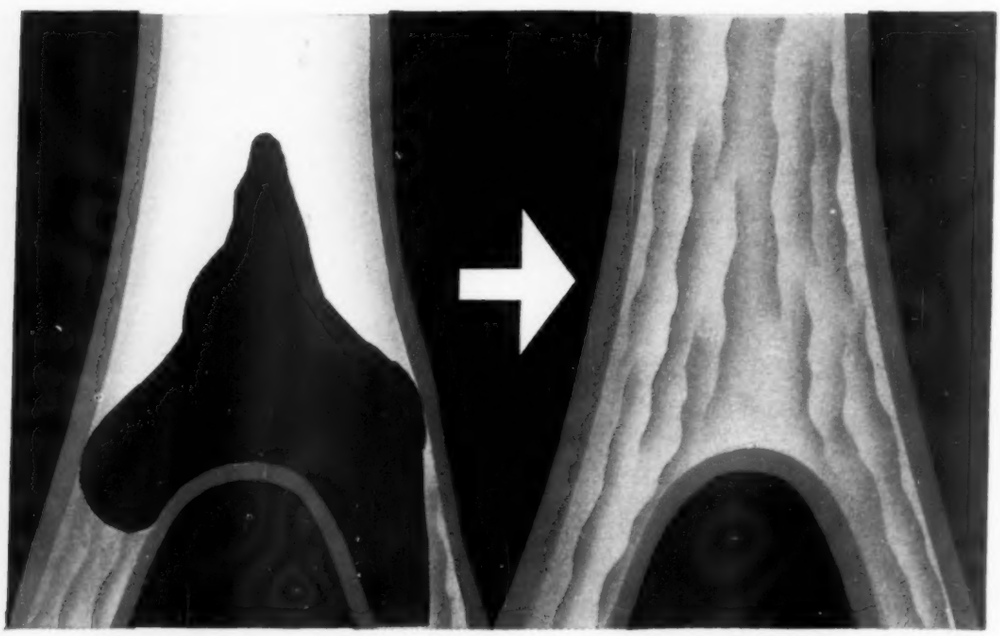
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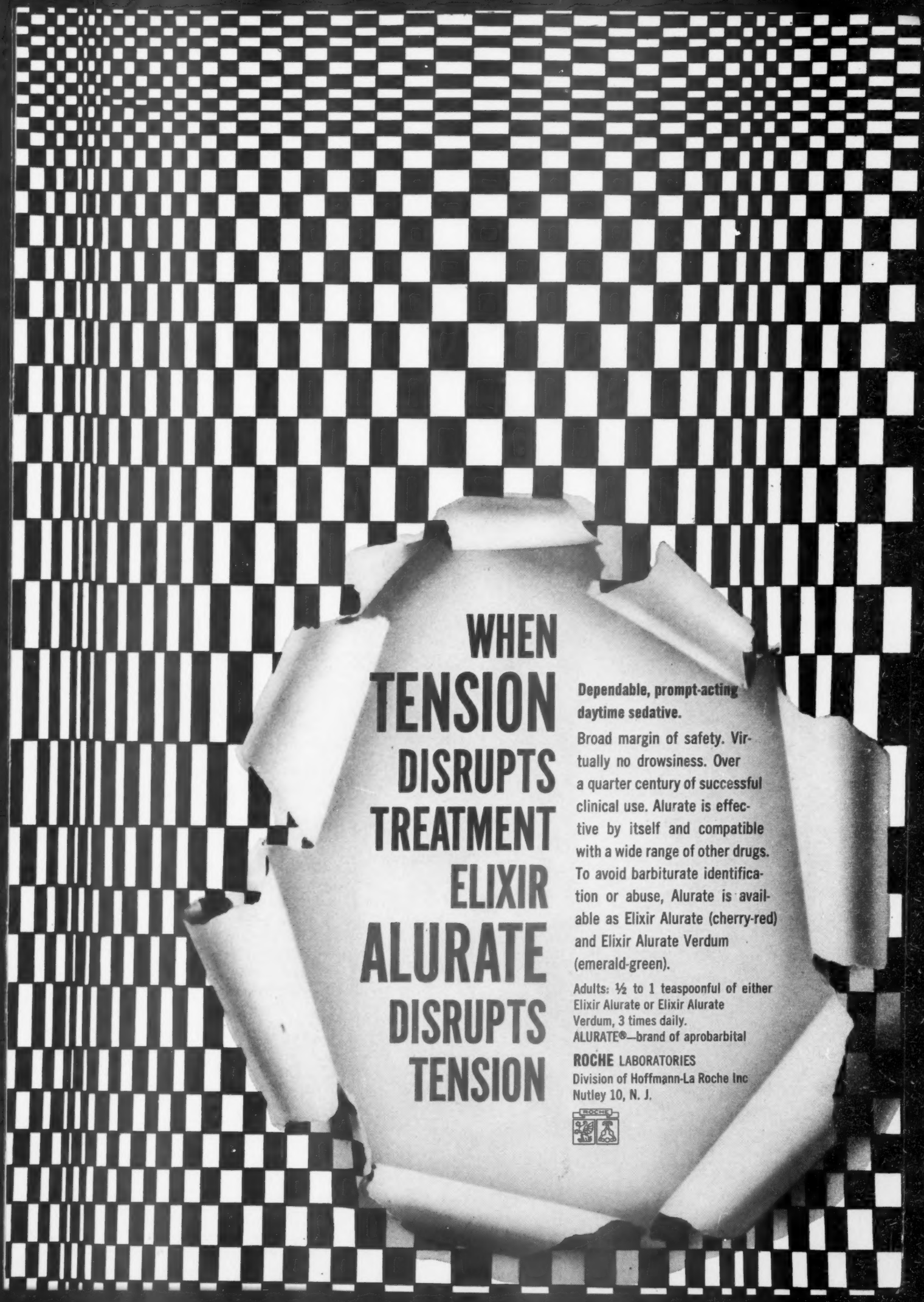
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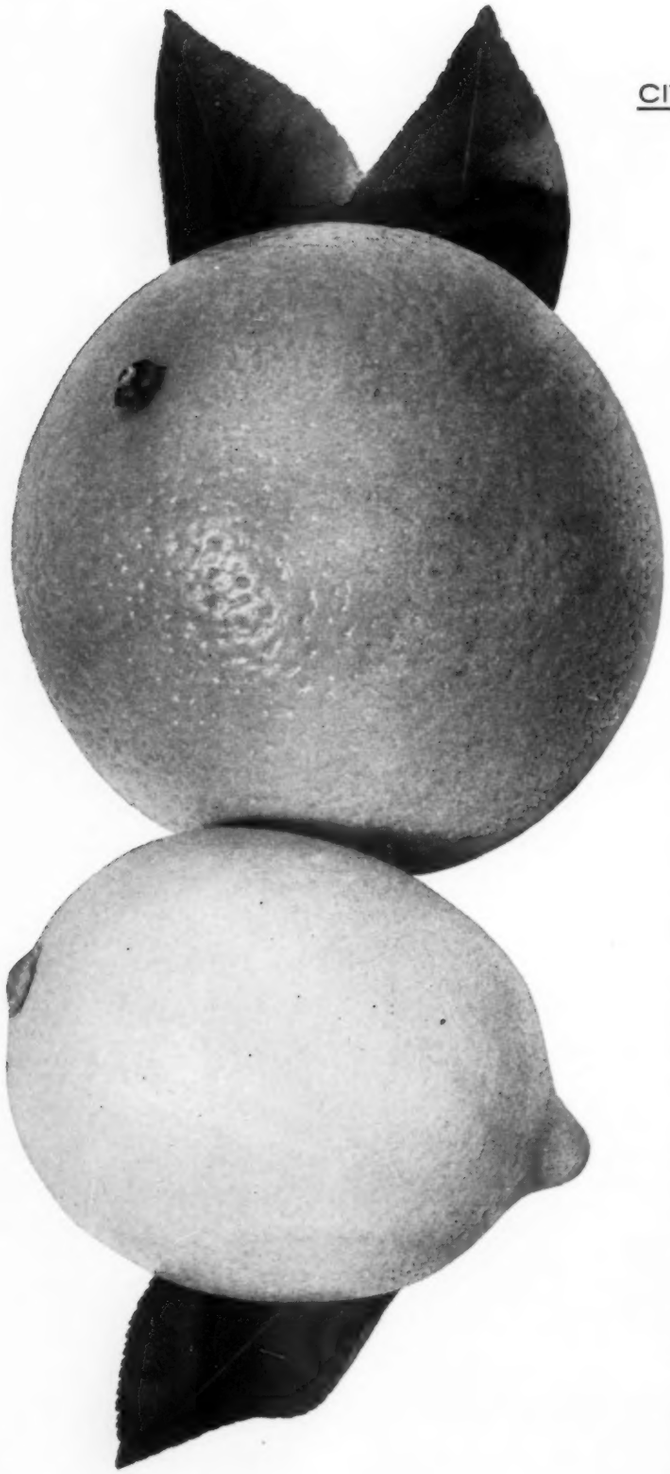
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Reports show older people have a high incidence of capillary fragility (6). In a group of 111 patients, capillary weakness was noted to be greatest in the fifth and sixth decades (5).

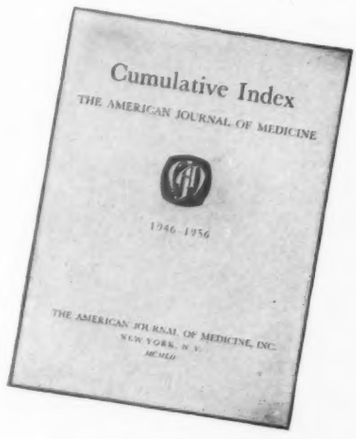
Hypertensives (7, 8, 9) and those with chronic diseases such as arteriosclerosis, diabetes and rheumatoid arthritis, have shown varying degrees of capillary involvement. Hemorrhagic conditions of the brain and heart have shown localized injury in the capillary (10, 11).

Capillary fragility has been shown to be associated with many bacterial, viral and inflammatory diseases (12-23).

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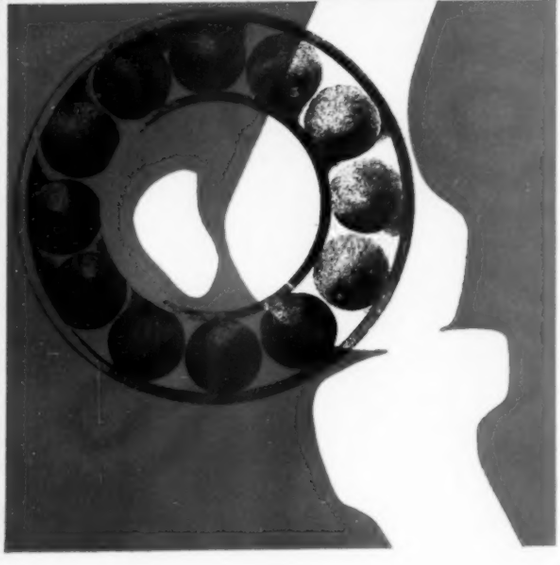
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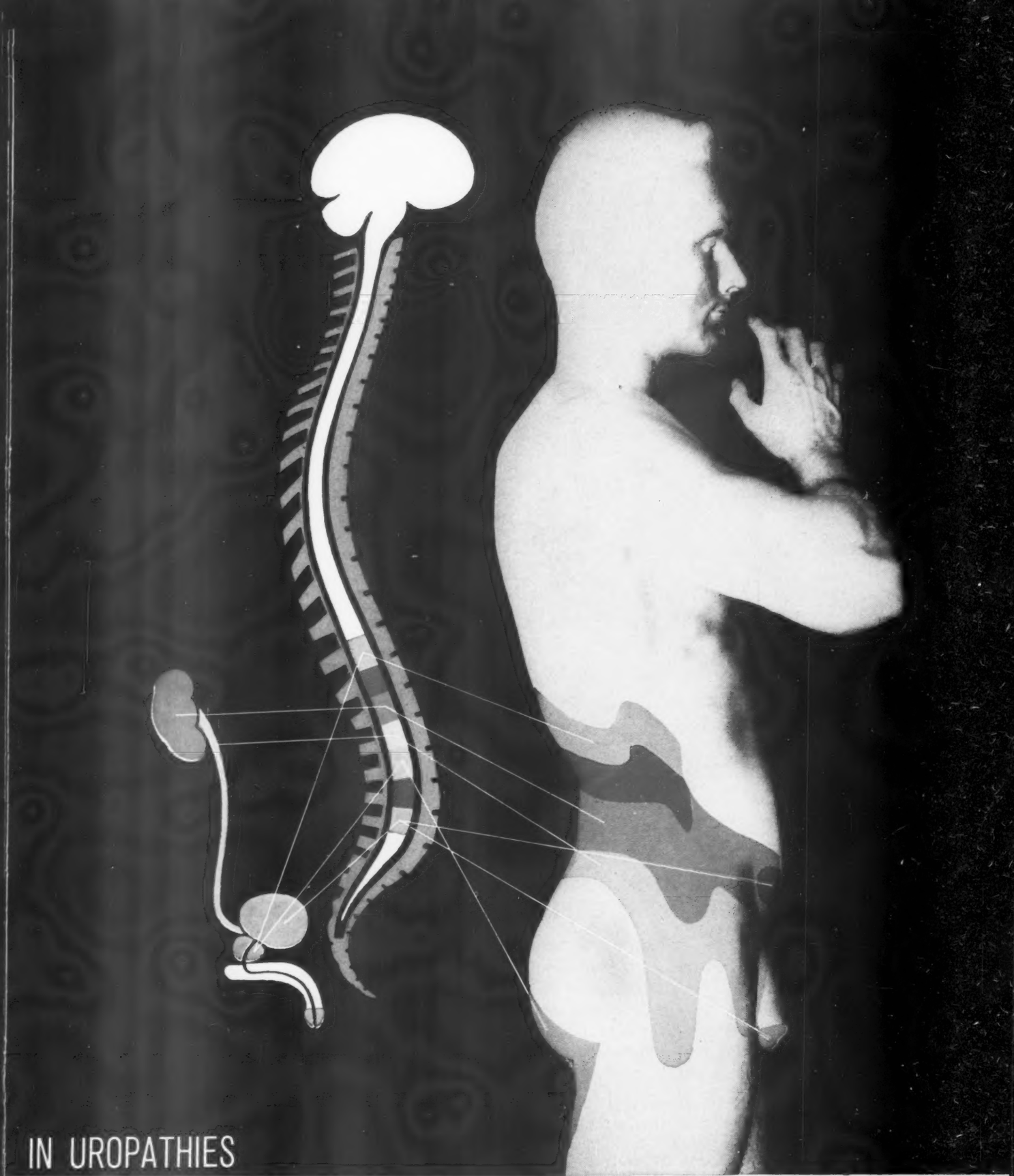
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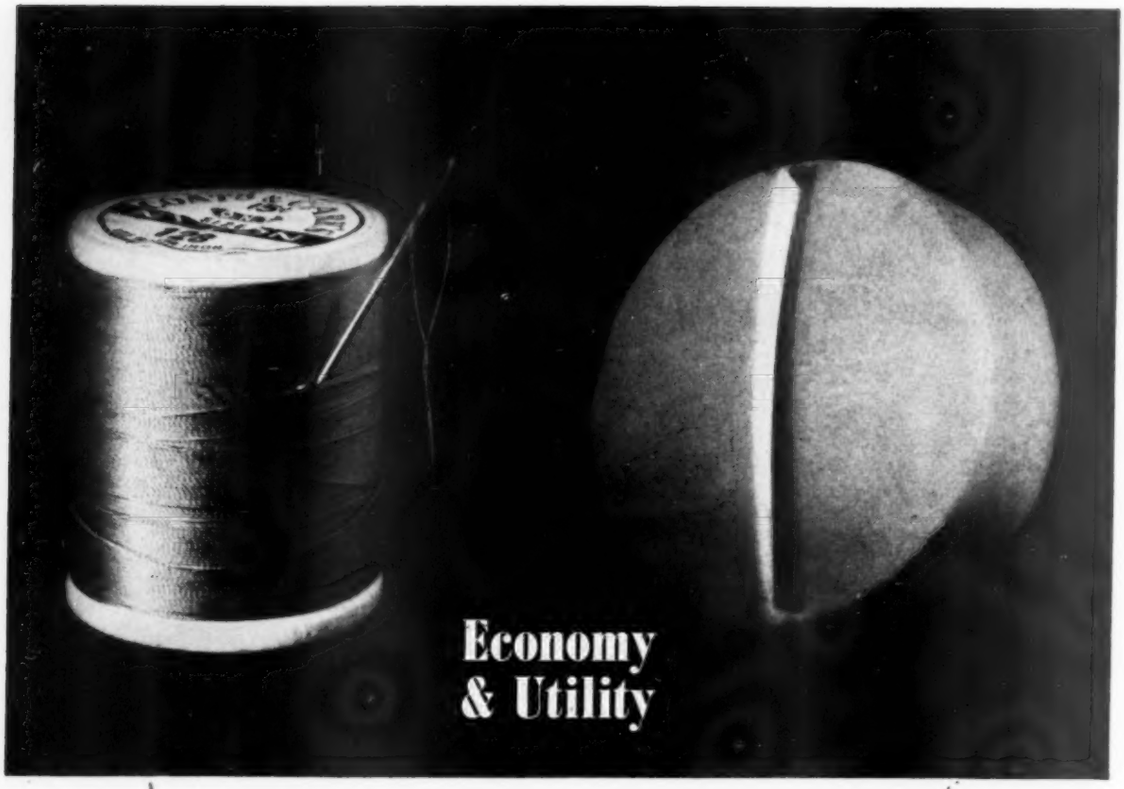
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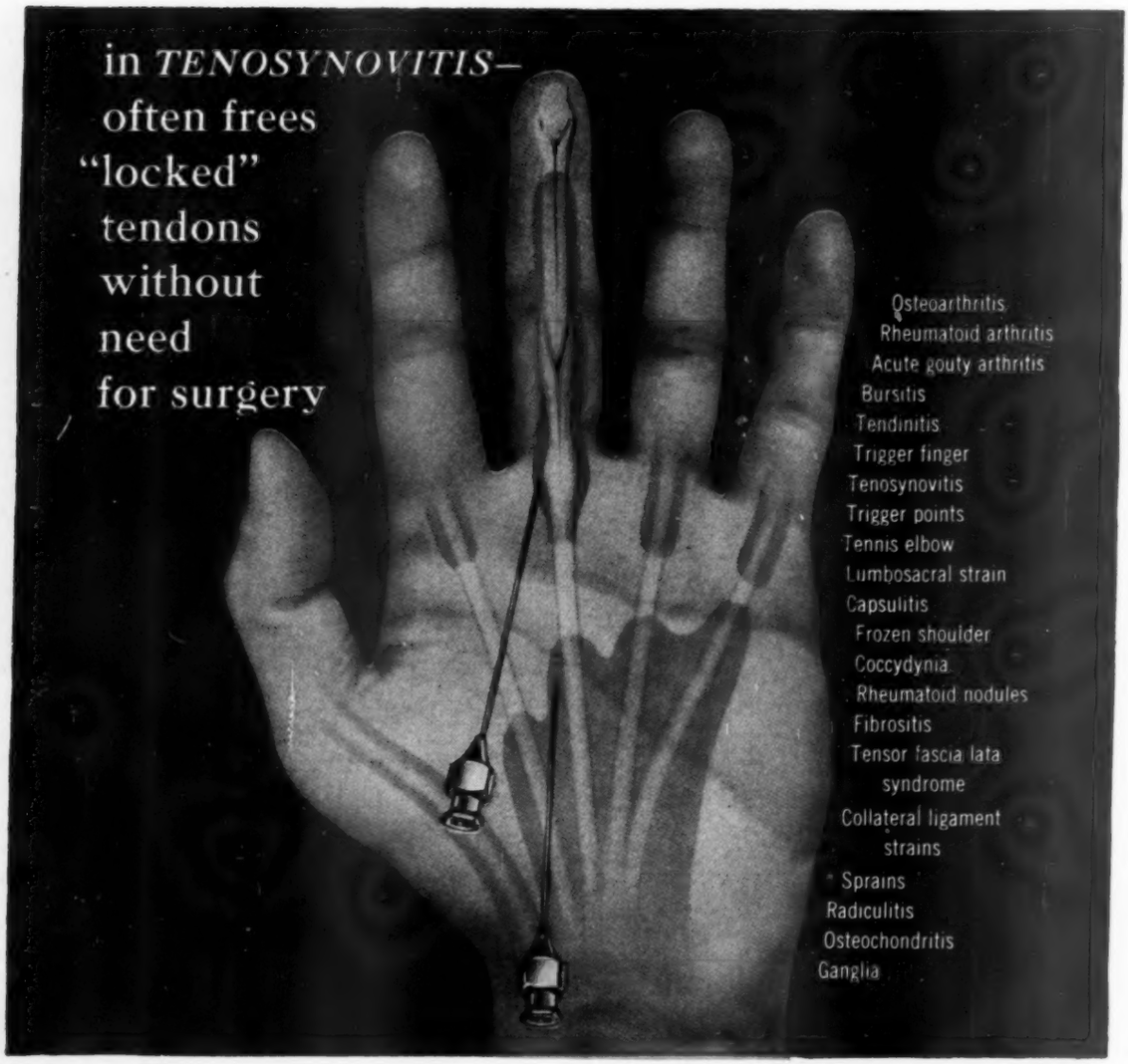
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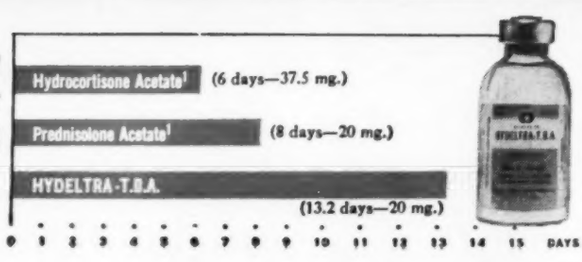
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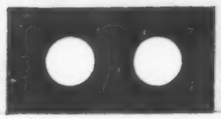


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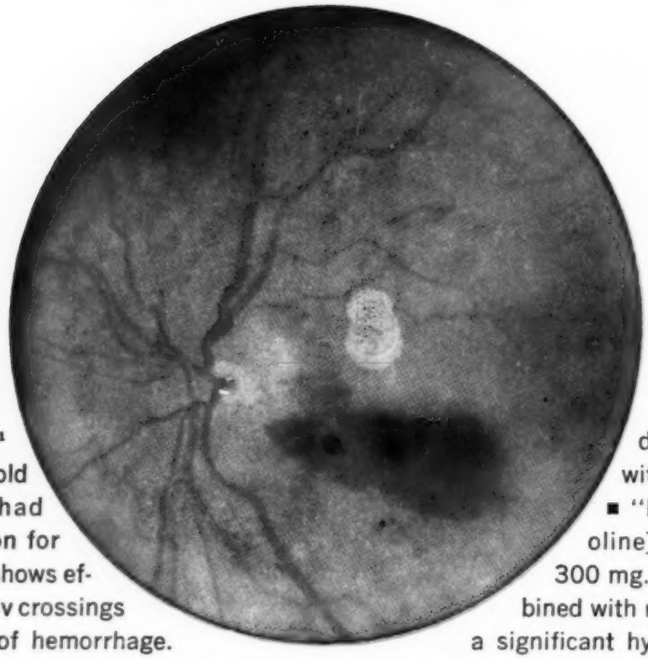
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1. Bedell, A. J.: Clin. Symposia **9**:135 (Sept.-Oct.) 1957.
2. Lee, R. E., Seligman, A. M., Goebel, D., Fulton, L. A., and Clark, M. A.: Ann. Int. Med. **44**:456 (March) 1956.

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